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THE WESTERN Journal of Medicine

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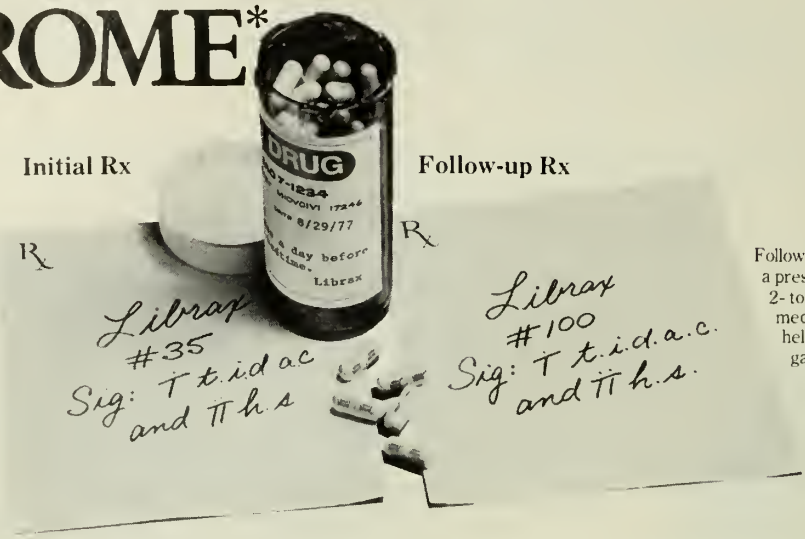

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"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl/Roche) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

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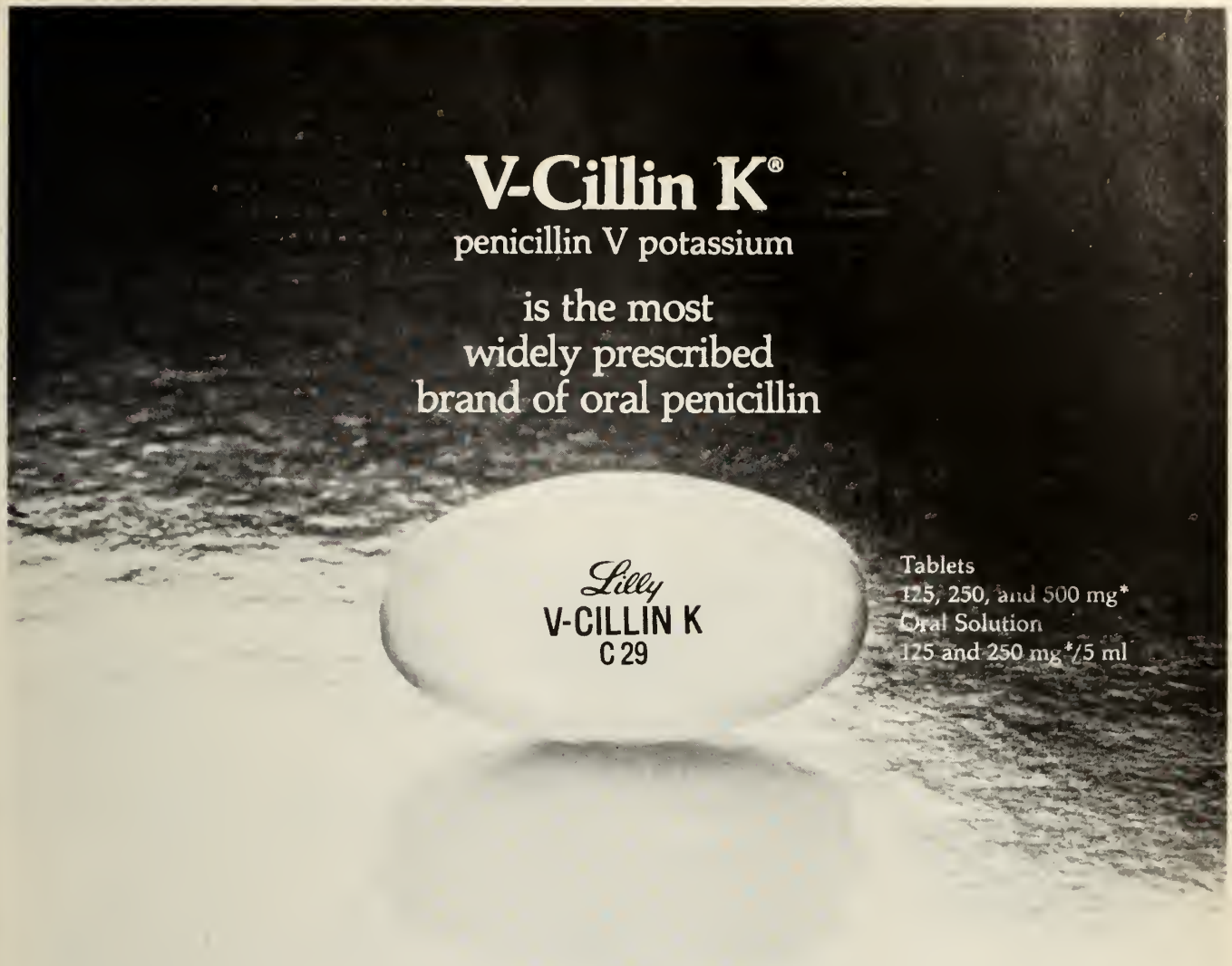

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Contraindication: Previous hypersensitivity to penicillin.

Warnings: Serious, occasionally fatal, anaphylactoid reactions have been reported. Some patients with penicillin hypersensitivity have had severe reactions to a cephalosporin; inquire about penicillin, cephalosporin, or other allergies before treatment. If an allergic reaction occurs, discontinue the drug and treat with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

Precautions: Use with caution in individuals with histories of significant allergies and/or asthma. Do not rely on oral administration in patients with severe illness, nausea, vomiting, gastric dilatation, cardiospasm, or intestinal hypermotility. Occasional patients will not absorb therapeutic amounts given orally. In streptococcal infections, treat until the organism is eliminated (minimum of ten days). With prolonged use, nonsusceptible organisms, including fungi, may overgrow; treat superinfection appropriately.

Adverse Reactions: Hypersensitivity, including fatal anaphylaxis. Nausea, vomiting, epigastric distress, diarrhea, and black, hairy tongue. Skin eruptions, urticaria, reactions resembling serum sickness (including chills, edema, arthralgia, prostration), laryngeal edema, fever, and eosinophilia. Infrequent hemolytic anemia, leukopenia, thrombocytopenia, neuropathy, and nephropathy, usually with high doses of parenteral penicillin. (102175)

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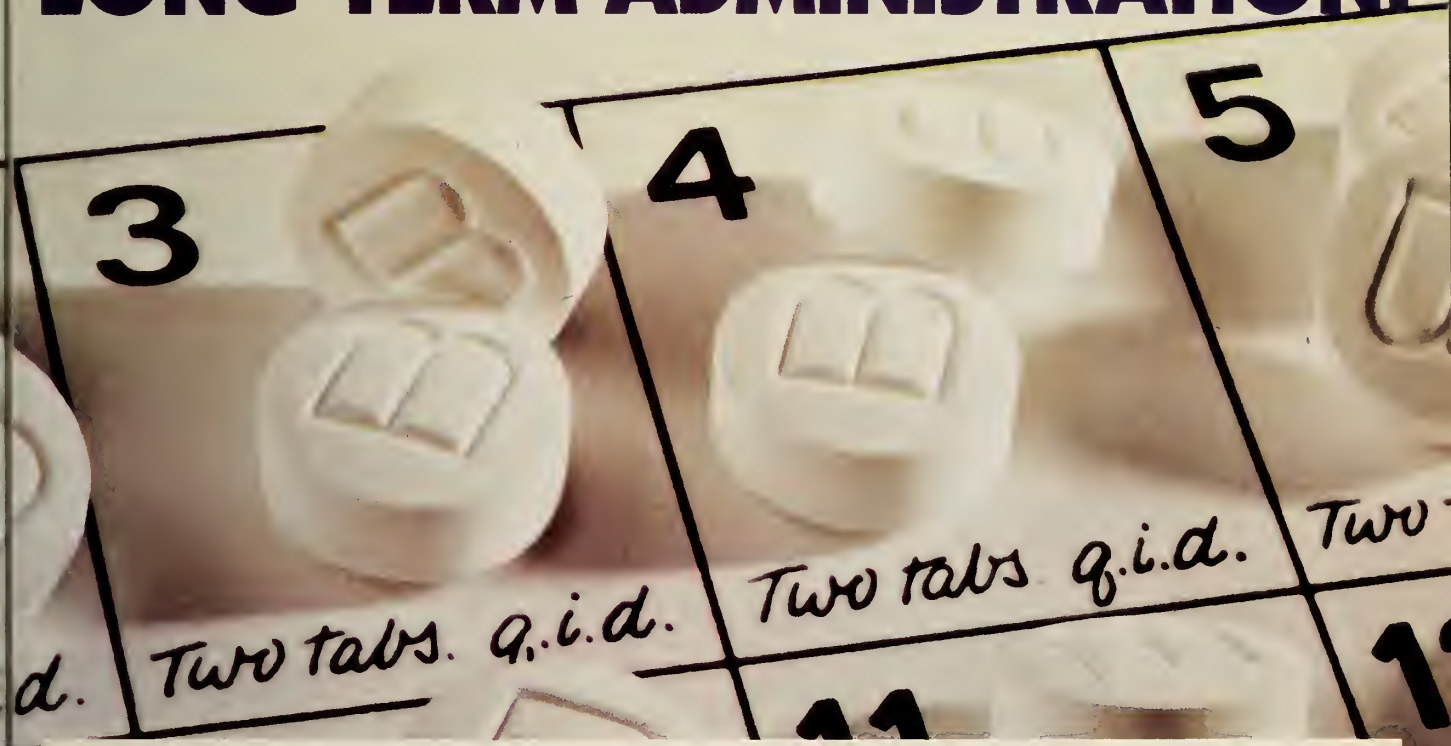

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on

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Twelve to sixteen internationally recognized scientists will present lectures on their work in these areas.

Registration fee for the meeting is $25.00 per participant ($10.00 for students). Lodging is available immediately adjacent to campus.

For registration and further information please write:

Endocrinology Symposium
Department of Biochemistry
University of California
Riverside, CA 92521

Phone (714) 787-4229

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances; anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular

Effectiveness in long-term use, i e , more than 4 months, has not been assessed by systematic clinical studies Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma

Warnings: Not recommended in primary depressive disorders or psychoses As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants

Physical and Psychological Dependence Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating) Addiction-prone individuals, e g drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated, anxiety, agitation, irritability, tension, insomnia and occasional convulsions

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg kg day No effect dose was 1 25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg day) Effect was reversible only when treatment was withdrawn within 2 months of first observation Clinical significance is unknown, but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G I disease

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS Some patients have developed leukopenia, some have had elevations of LDH As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study No studies regarding mutagenesis have been performed.

PREGNANCY Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide

NURSING MOTHERS It is not known if oral lorazepam is excreted in human milk like other benzodiazepines As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose In a sample of about 3,500 anxious patients most frequent adverse reaction is sedation (15 9%), followed by dizziness (6 9%), weakness (4 2%) and unsteadiness (3 4%) Less frequent are disorientation, depression, nausea change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U S P Usefulness of dialysis has not been determined

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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Philadelphia, PA 19101

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Why one benzodiazepine and not another?

Are you concerned about long-acting metabolites? Many clinicians, as well as pharmacologists, are beginning to draw attention to this problem (see New England Journal of Medicine, April 5, 1979).

In contrast to some older benzodiazepines, Ativan (lorazepam) does not give rise to long-lasting active metabolites. As with all benzodiazepines, you should follow the usual precautions concerning co-administration with other CNS depressants and warn your patients against operating dangerous machinery and motor vehicles.

However, it is noteworthy that Ativan showed no clinical evidence of accumulation even when given in high doses over periods up to 6 months. The half-life of free lorazepam is about 12 hours; steady-state serum levels are attained in 2-3 days. Comparable data for diazepam: 20-50 hours and at least 7-10 days. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Ativan has a convenient b.i.d. or t.i.d. dosage schedule; it is compatible with a long list of other medications and, of course, it is a highly effective anxiolytic agent, as established in numerous nationwide, double-blind, controlled evaluations in thousands of patients.

See important information on preceding page.

Ativan® (IV)
(lorazepam)
for Anxiety

A well-tolerated, nonnarcotic prescription for pain

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Motrin® now proved an effective analgesic for mild to moderate pain

Motrin 400 mg provided greater relief of pain than did propoxyphene 65 mg in controlled clinical pain studies.

Time after drug administration (hour)		.5	1	2	3	4
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	Darvon 65 mg propoxyphene	.66 (100)	.99 (99)	1.13 (96)	.99 (96)	.80 (96)
Statistical significance		$p<0.02$	$p<0.01$	$p<0.05$	$p<0.02$	$p<0.002$

*0 = No relief 1 = Partial relief 2 = Complete relief

Data on file at The Upjohn Company

Motrin demonstrated statistically significant greater relief of pain than did Darvon at all time intervals.

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- Not a narcotic • Not addictive • Not habit forming
- Rapid analgesic action • Indicated in acute and chronic pain
- Well tolerated. The most common side effect with Motrin is mild gastrointestinal disturbance.

Please turn the page for a brief summary of prescribing information.

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Motrin® (ibuprofen)
now proved an effective analgesic for mild to moderate pain

Motrin® Tablets (ibuprofen, Upjohn)

Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Relief of mild to moderate pain.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

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Drug interactions. *Aspirin:* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness,* headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

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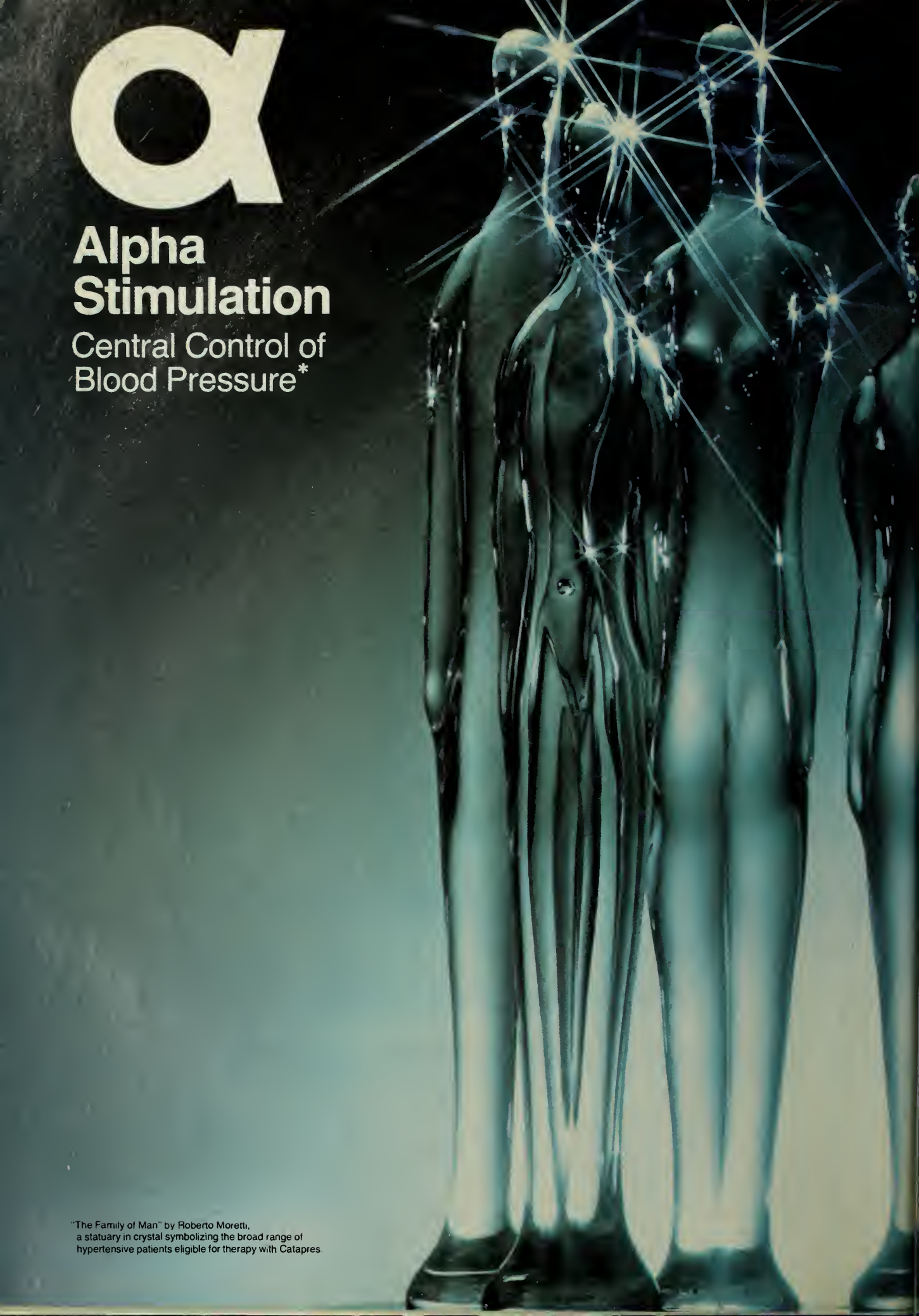

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*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

1 Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

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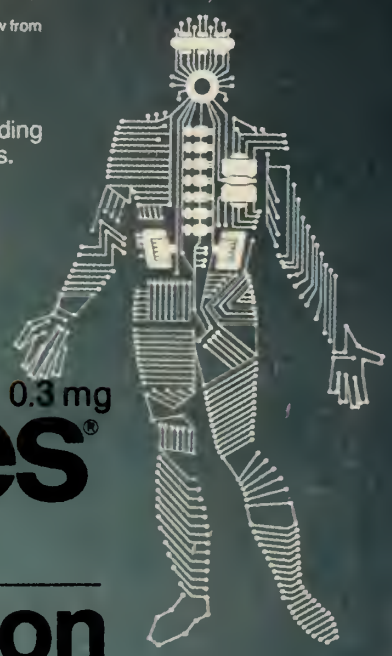

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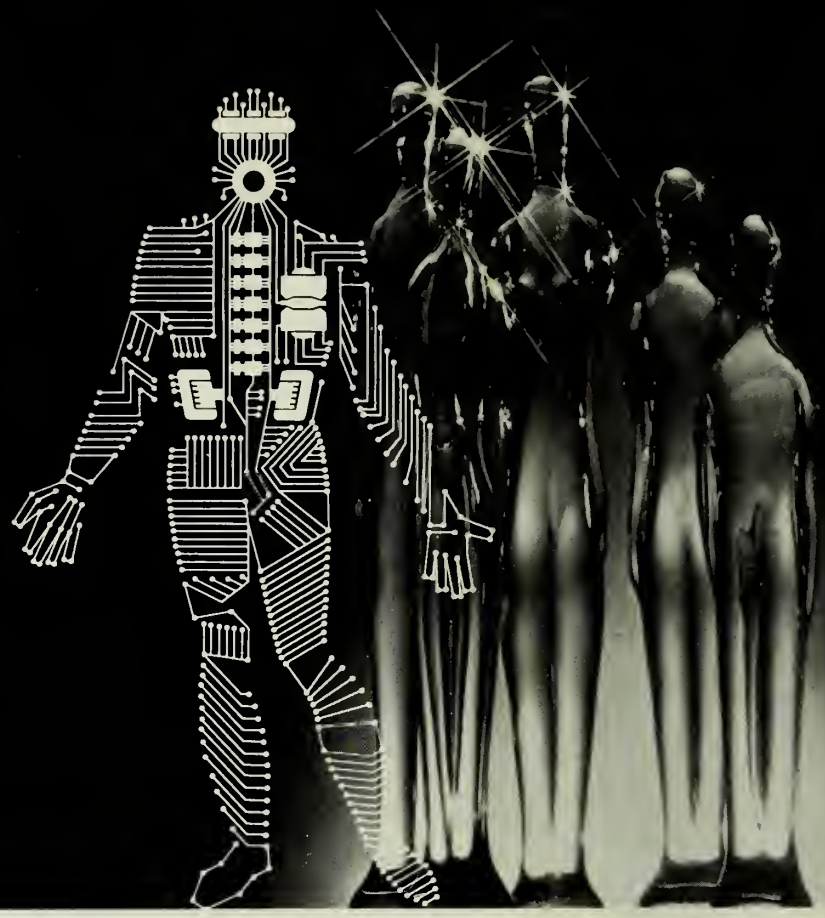

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Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness a sedation. Constipation, dizziness, headache, and fatigue have been reporte Generally these effects tend to diminish with continued therapy. The followi reactions have been associated with the drug, some of them rarely. (In som instances an exact causal relationship has not been established.) These includ Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities liver function tests; one report of possible drug-induced hepatitis without icter and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlo thalidone and papaverine hydrochloride. Weight gain, transient elevation of bloo glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud phenomenon; vivid dreams or nightmares, insomnia, other behavioral change nervousness, restlessness, anxiety and mental depression. Also rash, a gioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associate with a rash, impotence, urinary retention, increased sensitivity to alcohol, drynes itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomasti weakly positive Coombs' test, asymptomatic electrocardiographic abnormaliti manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or a sent reflexes and vomiting followed the accidental ingestion of Catapres (clonidi hydrochloride) by several children from 19 months to 5 years of age. Gast lavage and administration of an analeptic and vasopressor led to complete r covery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minu intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) ove dosage.

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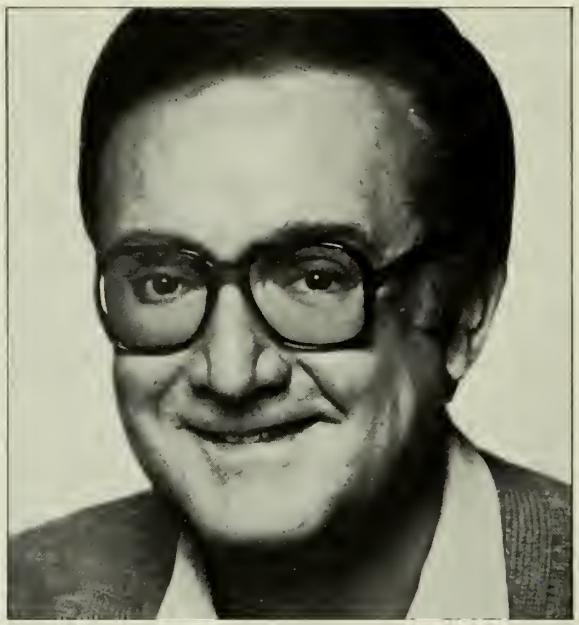

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Portion Size 1 Fluid Ounce (2 Tbs.)

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Calories	40
Protein	0 grams
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Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol (Δ) (0 mg/100g)	0 mg

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THE WESTERN
Journal of Medicine

Refer to: Simonowitz DA: The operative management of Crohn disease. West J Med 132:1-6, Jan 1980

The Operative Management of Crohn Disease

DAVID A. SIMONOWITZ, MD, *Seattle*

The natural history of Crohn disease is varied and unpredictable, and its cause is not known. No modality of treatment has definitely been shown to alter its course.*

Surgical treatment was carried out in a consistent fashion in 141 consecutive patients with Crohn disease. The indications for surgical operation were the complications of the disease only; these included fistula, abscess, obstruction and hemorrhage. Preoperative evaluation included upper gastrointestinal examination, barium enema, intravenous pyelogram, proctoscopy, and nutritional and volume support. In 76 of these patients previous operations had been carried out for Crohn disease.

The surgical treatment was based upon the specific complication present, with adherence to the principle of resection of diseased tissue only. Ureterolysis also was necessary in 20 percent of these patients. The operative mortality was 1.4 percent, postoperative complications occurred in 54 patients and the surgical recurrence rate was 26 percent. A favorable result was accomplished in 85 percent of the patients.

THE NATURAL HISTORY of Crohn disease* is unpredictable. The cause is unknown and no modality of treatment has been shown to alter its varied course. This report deals with the surgical approach to Crohn disease from the perspective of a patient presenting to a surgeon for the first time—regardless of previous surgical treatment.

From the Department of Surgery, University of Washington School of Medicine, Seattle.

Submitted, revised, July 25, 1979.

*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

Reprint requests to: David A. Simonowitz, MD, Dept. of Surgery, RF-25, University of Washington, Seattle, WA 98195.

Early operation is advocated for complications of Crohn disease such as fistula, sinuses, abscesses, obstruction, growth retardation or hemorrhage. Intensive preoperative preparation includes adequate correction of blood volume, protein, osmolarity, iron and vitamin deficiencies. Whenever possible a thorough mechanical bowel preparation, along with administration of antibiotics orally, is carried out. The operative approach is conservative resection and primary anastomosis when suitable.

Recurrence in patients with regional enteritis is well documented and frequent.[1] In this review,

TABLE 1.—*Laboratory Findings in 141 Patients with Crohn Disease*

Average Preoperative Weight 54.03 kg	*Percent*
Sideropenia	73
Hypoproteinemia	49
Hypoalbuminemia	56
Anemia	44
Leukocytosis	43
Hematuria or pyuria	18
Abnormal liver function tests	8

recurrence is used to mean recurrence after the initial operative treatment by the authors. If a two-stage initial operative approach was used, the second stage is not considered an operative recurrence of the disease.

Patients

In 141 patients with Crohn disease, surgical treatment was carried out by the same surgeons at the University of Chicago Hospitals from 1960 through 1974. The diagnosis of Crohn disease was based in all but three patients on the results of pathologic examinations of the surgical specimens. In the three exceptions, diagnosis was made because of radiologic evidence with concomitant severe rectal disease.

Of the 141 patients, 82 were male (58 percent). There were 15 black patients. The mean age of the patients was 28.8 years (range 9 to 61 years). The history of Crohn disease in these patients ranged from two months to 34 years, with an average of 6.7 years.

More than 80 percent of the patients presented with diarrhea, weight loss or cramps. In about 50 percent, stool specimens were positive for occult blood, or fevers were present or fistulae were noted either on physical examination or radiologic studies. A third presented with nausea and vomiting, or rectal disease, or a palpable abdominal mass. Laboratory findings are summarized in Table 1.

Preoperative proctoscopic examinations were carried out in 116 patients and findings in 58 were consistent with Crohn disease. Barium enema studies were done in 126 patients and in 77 percent of these the results were consistent with Crohn disease. These barium enema studies showed the following: fistula tracts to the colon in 18, pancolonic involvement in 25, right colon involvement only in 52 and left colon involvement in 20. In 129 patients small bowel radiologic contrast studies were done and in 91 percent the results were consistent with Crohn disease. Fistula tracts involving the small bowel were shown by 44 of these studies. In 109 patients upper gastrointestinal examinations were done and in five the findings were consistent with Crohn disease. Intravenous pyelograms were carried out in 99 patients and in 24 they showed either a right hydroureter or, in two cases, renal calculi.

TABLE 2.—*Primary Operations in 141 Patients with Crohn Disease*

	Operations
Ileotransverse colostomy and bowel resection	45
Ileostomy, mucous fistula and ileocolonic resection	29
Ureterolysis	29
Ileoascending colostomy and bowel resection	10
Ileosigmoidostomy and bowel resection	7
Total proctocolectomy	7
Ileotransverse colostomy, mucous fistula and bowel resection	7
Fistulectomy	6
Drainage of rectal abscess	5
Ileal resection	4
Drainage of abdominal abscess	3
Ileoproctostomy and bowel resection	2
Colostomy, mucous fistula and bowel resection	2
Ileoascending colostomy, mucous fistula and bowel resection	2
Duodenal bypass	1
Closure of perforation	1
Laparotomy	1
TOTAL	161

Initial preoperative management in most of these patients was uniform. Steroids were given to 68 percent, sulfasalizine to 76 percent, phenobarbital with belladonna to 42 percent, diphenoxylate to 28 percent and azathioprine to 7 percent. A total of 132 previous operations related to Crohn disease had been carried out in 76 of the patients (54 percent).

Operative Indications and Treatment

Most of the patients received elective operations. However, 12 underwent emergency operations. The indication for operative treatment was varied, but operations were always done for complications of Crohn disease. Of the 141 patients, 79 (56 percent) had fistula disease, 27 had infection or abscess formation (or both), 23 presented with obstructive symptomatology and 7 had had growth retardation as a consequence of the disease. In five patients massive rectal bleeding was the indication for operation.

The particular operations carried out were

TABLE 3.—*Postoperative Complications in 54 Patients with Crohn Disease*

	Patients
Prolonged ileus	10
Urinary tract infection	9
Wound infection	9
Intra-abdominal abscess	8
Upper gastrointestinal hemorrhage	4
Sepsis	4
Enterocutaneous fistula	3
Severe diarrhea	3
Colostomy revision	2
Pneumonia	2
Wound hemorrhage	2
Hepatitis	2
Ileostomy dysfunction	1
Decubitus	1
Adhesions with obstruction	1
Volvulus	1
Arrhythmia	1
Prolonged fever	1
Congestive heart failure	1
Herpes	1
TOTAL	66

functions of the specific manifestations of the disease. The basic philosophic concepts were resection of diseased bowel, open drainage of abscesses and limiting resection to the visible area of the pathologic conditions, although frozen sections were occasionally done. All anastomoses were done in two layers with interrupted silk sutures.

Bowel resection with a resulting ileotransverse colostomy (end to side) was done in 49 patients. This is the standard operative approach to Crohn disease limited to the terminal ileum and right colon. The other operations are summarized in Table 2. In addition, in 29 patients ureterolysis was also done to alleviate a right hydroureter.

Operative Findings and Results

The major findings noted in the resected bowels were as follows: 87 patients had enteroenteric fistulae, 27 had intra-abdominal abscesses, 24 had severe obstructive disease and three were noted to have hemorrhagic necrosis. The disease process was limited to the colon alone in 18 patients, small bowel alone in 7 and mixed colon and small bowel in 118.

A total of 66 postoperative complications occurred in 54 patients. These complications are summarized in Table 3. The most common problem was postoperative ileus of greater than five days; this occurred in ten patients.

In 75 patients a second operation was carried out. This was not necessarily due to recurrence of the disease, as noted by the fact that the most frequent such operation was an anastomosis of an "ostomy" and a mucous fistula. In 36 of these patients a tertiary operative procedure was done, in four a sixth procedure, in two a seventh procedure, in two an eighth procedure, in one a ninth procedure and in one a tenth procedure.

When the operative procedures were excluded that were not due to a recurrence of Crohn disease but rather to the nature of the initial operative procedure or its inherent complications, there were 105 patients (74 percent) in whom only one operative treatment for the disease was required. Five of these died, a mortality of 4.7 percent. In 11 (10.4 percent) there was documented radiologic recurrence of disease while in two others there was clinical recurrence with negative radiologic findings.

In 23 patients (16 percent) two operative procedures were required because of recurrence of disease. Two of these died, a mortality of 8.6 percent. In five there was a recurrence of symptoms, and in one of these the radiologic findings were negative.

Tertiary operations because of recurrent disease were carried out in ten patients (7 percent). There were clinical recurrences in four in this group and in one of these radiologic findings showed no abnormalities. There were no deaths in this group. More than three operations for recurrence of regional enteritis were required in three patients—in all of whom there was documented postoperative recurrence.

The follow-up period for these patients ranges from 1 to 149 months, with an average of 32.7 months. The average weight gain in this period was 6.7 kg. At present, 55 patients (39 percent) are receiving steroids, sulfasalazine or antispasmatics for recurrent symptoms. Recurrent abdominal symptoms are present in 22.

Excluding the eight who have died, there is a clinical recurrence of disease in only 22 patients (15.6 percent). In 18 of these patients radiologic findings are positive. Two have symptoms with negative roentgenograms, but both have fistulae. Two have vague symptoms with negative roentgenograms and no physical evidence of recurrence.

There were eight postoperative deaths. Only two of these occurred within 30 days of the operation, an operative mortality of 1.4 percent. Both of these patients died of intra-abdominal sepsis. Five died three months after operation.

The causes of death were severe dehydration, liver failure, renal failure, myocardial infarction and suicide.

One died one year postoperatively from a cerebral vascular accident and metastatic carcinoma. Of the eight deaths in this series four patients died following an emergency operation. Two deaths were due to technical errors and these were potentially avoidable (in one a mucous fistula became necrotic and was not treated promptly; in the other an anastomotic leak developed from inappropriate bowel closure), and two other deaths were not due to operative treatment (metastatic carcinoma in one and suicide in the other).

Discussion

There are few reliable studies on the natural history of Crohn disease. This is due to the chronic and varied nature of the disease. There are also few reports of large numbers of patients in personal consecutive series of operative and medical management.

The basis of this report is the concept that the initial treatment by surgeons represents the baseline for the management of the disease, irrespective of previous operative treatment. This frame of reference also has been used by others[2-6] because this is the manner that patients actually present to surgeons.

The epidemiologic characteristics and clinical presentation of the patients in this report are similar to those in other reports.[3,7,8] In these patients, however, there was a higher incidence of occult blood in stool specimens, fevers and fistulae than in patients in other reports.[2,5-10]

These data tend to support the work of Cooke[11] in that correlates of Crohn disease activity appear to be weight loss, hypoalbuminemia, anemia and sideropenia. These are not direct relationships but are useful guides in patient management.

The surgical approach to the operative management of Crohn disease begins with a detailed and careful preoperative evaluation. Intensive radiologic examinations are used to ascertain the extent of the disease. In particular, intravenous pyelography is required because patients with the disease not infrequently have an obstructive uropathy.[12] Preoperative preparation is planned to correct the patients' biochemical abnormalities and supplement their medical treatment, as has been previously reported.[13,14] In most of these patients there have been previous operations which have exposed the chronic nature of the disease and make it essential that operative treatment be deliberate and carried out by experienced surgeons.[2,7,15]

Complications of Crohn disease are the indications for operation. These complications vary in frequency of occurrence[2,8,10] and include fistulae, abscess, obstruction, growth retardation, intractability and hemorrhage. We note a 5 percent incidence of rectal hemorrhage as an operative indication; this finding is at variance with those of other reports.[2,16] Emergency operation is not usually necessary in patients with Crohn disease because most complications are amenable to initial medical management.[11]

The surgical management of patients with Crohn disease is concerned intimately with surgical technique because of the recurrent nature of the disease. The author advocates conservative resection of bowel, with primary anastomosis when suitable, using a two-layer anastomosis of nonabsorbable suture.[17] This is in opposition to those who advocate radical resection.[5,18,19] The operation is individually tailored to the specific complication and the state of a patient's health; nevertheless, postoperative complications frequently occur in this chronic inflammatory disease.[15,20] The hydroureter associated with Crohn disease is due to a localized perforation of the bowel with a resulting retroperitoneal inflammation causing constriction of the ureter. The operative approach to this entity in its chronic form is that of resection of the diseased bowel and ureterolysis. If frank pus is found, the bowel is temporarily exteriorized and the abscess is drained. Similarly, with fistulae or abscess formation, the diseased segment of bowel is resected and then, depending upon the amount of inflammation, the bowel is exteriorized or anastomosed with or without drainage.

The results of the surgical management of Crohn disease can be judged in three ways.[4,21] First is operative or surgical mortality. Second is the need for repeated surgical treatment because of disease recurrence. Third is symptom recurrence. This latter category is somewhat vague but has been well delineated in a paper by Lennard-Jones.[4] It is documented that the rate of recurrence is highest within two years of operation but continues to occur as a function of time.[1,22-24] The recurrence of Crohn disease in the patients after operation is not as incapacitating as would be expected; this is because these patients are

TABLE 4.—*Published Surgical Recurrence Rates of Crohn Disease*

	Percent Surgical Recurrence		
Reference	*2nd Operation*	*3rd Operation*	*4th Operation*
1	58.0	..	..
2	26.5	32	33
3	27.0	..	..
5	25.0	26	22
7	18.0	..	..
8	28.0	25	..
9	50.0	50	..
15	20.6	..	..
18	22.0	30	..
20	25.0	20	33
21	34.0	..	..
23	15.2	..	..
24	26.0	..	..
27	22.0	..	..
29	52.0	..	..

TABLE 5.—*Published Nonsurgical Recurrence of Crohn Disease Following Operation*

Reference	*Percent Recurrence*	*Reference*	*Percent Recurrence*
1	23	20	30
4	28	23	23
5	39	25	54
15	37	28	35
18	30	29	40

generally in better health than they were preoperatively.[2,20,25,26]

In assessing the results of our operative approach, an increased average postoperative weight gain of 7 kg is first noted. Another method of assessing operative results in the follow-up period is to compare the number of patients being treated with medications preoperatively versus postoperatively. Of our patients, 55 (39 percent) at present are receiving steroids, anticholinergics or sulfasalizine; preoperatively this percentage was near 80.

The operative mortality of this series was 1.4 percent (two patients). Both deaths were due to sepsis. Five patients died 60 to 90 days postoperatively; all but one as a complication of the disease. One patient died a year postoperatively of carcinoma. Thus, the total mortality is 5.6 percent. Four of these eight deaths followed an initial emergency operative procedure. These statistics compare favorably with those in other reports and support this philosophy of the operative management of Crohn disease. In this series, in 105 patients (74 percent) only one operation was needed for treatment of the disease. In 26 percent more than one operation was required for recurrence of disease. In 16 percent only two operative procedures were required and in 10 percent three or more operations were needed.

Again, the proposed operative philosophy yielded a surgical recurrence rate of 26 percent and a rerecurrence rate of 43 percent, with the risk of a third operative recurrence of 33 percent. These results also compare well with those reported in the literature (Table 4).

The last method in assessing recurrence is to ask the following question: At the end of the follow-up period how many patients are symptomatic? These patients can then be divided into two groups: those with objective signs of recurrence and those with only subjective signs of recurrence. Of the patients, 15.6 percent at present are symptomatic after an average follow-up of 33 months. In 13 patients there are objective signs of recurrence. One patient refused a resection and in another resection was impossible because of the extent of the disease. These statistics compare favorably with other reported results (see Table 5).

Conclusion

A consecutive series of 141 patients with Crohn disease requiring operative treatment has been reviewed. A philosophy of surgical care, technique and management for the operative treatment of complications of Crohn diease is offered. It resulted in an operative mortality of 1.4 percent and a favorable end result in 85 percent of patients. The surgical treatment is not curative but is dramatically restorative. Conservative resection and operation for only the complications of Crohn disease after intensive medical management are the hallmarks of this treatment.

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The Development of Asbestosis

IT IS POSSIBLE to have asbestosis from a single—a few weeks or months—very large exposure because there is no way that the asbestos fibers can be eliminated from the lung. Asbestos disease is very, very slow in developing—almost never does anything happen for 15 years, and that makes diagnosis very difficult; and makes it difficult for industrial hygienists because every time they improve a situation in a plant, they have to wait 15 or 20 years to see what will happen.

—EDWARD A. GAENSLER, MD, *Boston*

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Refer to: Stegman SJ, Tromovitch TA: Modern chemosurgery—Microscopically controlled excision. West J Med 132: 7-12, Jan 1980

Modern Chemosurgery—Microscopically Controlled Excision

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Chemosurgery is no longer the slow, painful, last-resort technique for skin cancer. With recent modifications the chemosurgery method, now called microscopically controlled excision (MCE), retains the careful microscopic tracing of even the smallest tumor strands but avoids the morbidity of zinc chloride paste. So far, the cure rate for microscopically controlled excision of difficult, recurrent or large basal cell carcinomas is comparable with that obtained by the classic procedure. This modification is more adaptable to current concerns for cosmesis, cross-specialty usage and early treatment for lesions known to have poor cure rates by standard modalities.

THERE ARE SEVERAL adequate ways to treat skin cancer today: curettage and desiccation, radiation therapy, standard surgical excision, cryotherapy and, more recently, the use of laser beam and 5-fluorouracil. These methods have varying cure rates, but for well-defined primary basal cell carcinoma or squamous cell carcinoma the cure rate can be well over 90 percent when standard methods are used. However, the use of curettage and desiccation, radiation therapy or surgical excision carries a cure rate of only about 50 percent if reapplied to a lesion that has *recurred* after the use of any one of these three modalities[1,2] (Figure 1).

Two characteristics of basal cell carcinoma contribute highly to the recurrence rate. First, basal cell carcinoma has the proclivity to send out strands of tumor well beyond the central mass. These narrow strands can extend several centimeters and travel in periosteal and perichondrial planes, along neurovascular bundles or just above the galea of the scalp. The presence of these strands and the ability of basal cell carcinoma to grow egocentrically lead to unsuspected recurrences of the tumor. Second, the morphea or sclerosing type of basal cell carcinoma is composed of many small strands of tumor throughout the dermis and subcutaneous tissue. These tumors have indistinct clinical margins, rarely show elevation above the normal skin level and may grow undetected for many years. These criteria present a clear need for selecting a microscopically controlled method to eradicate difficult or recurrent skin tumors.

In the late 1930's Dr. Frederic Mohs of Madison, Wisconsin, developed a technique in which he applied zinc chloride paste over the suspected area of tumor and fixed it in vivo.[3] He excised only the fixed tissue, sectioned it into small pieces, drew a map of the pieces so he could refer to the exact anatomic location on the patient, dyed the edges of the pieces so that under the microscope they could be properly oriented, cut *horizontal* frozen sections from the undersurface and then

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stained them with hematoxylin and eosin. The technique allowed him to visualize microscopically the entire lateral and undersurface of the excised tissue. This method became the classic chemosurgical procedure which has had a long and successful history in the United States and throughout the world.[4]

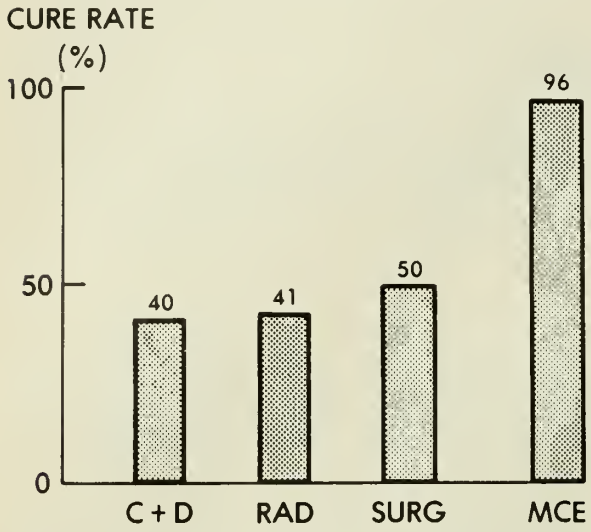

Figure 1.—Treatment of recurrent basal cell carcinoma. The cure rate for a recurrent basal cell carcinoma is significantly reduced when treated by curettage and desiccation (C + D), radiation therapy (RAD), surgical excision (SURG). The microscopically controlled excision (MCE) method is able to produce a cure rate of 96 percent or higher for recurrent skin tumors. (Adapted from data published by Menn et al.[1])

Although classic paste-fixation chemosurgery is very successful for skin tumors, including recurrent tumors and difficult sclerosing tumors, it is often time consuming for both patient and physician and involves much pain for the patient. Inherent within the method is the need for a final slough of the in vivo fixed tissues which means that all wounds must first be allowed to heal by secondary intention before later surgical scar revision can be undertaken. A modification of the Mohs chemosurgery, first published by Tromovitch and Stegman[5] in 1974, bypasses the zinc chloride fixation, thus eliminating that painful step. This paper presents the modified chemosurgical technique, its cure rates, and its advantages and disadvantages as a procedure.

Modified Chemosurgery—Fresh Tissue Technique

The fresh tissue technique (Figure 2) has been fully described previously,[5-7] but will be reviewed briefly here. The surgical procedure is almost always performed in an outpatient setting with the use of a local anesthetic. The tumor is first curetted to help discover and ferret out small strands and irregular excrescences of soft epithelial tumor growing in the firm, fibrous corium.

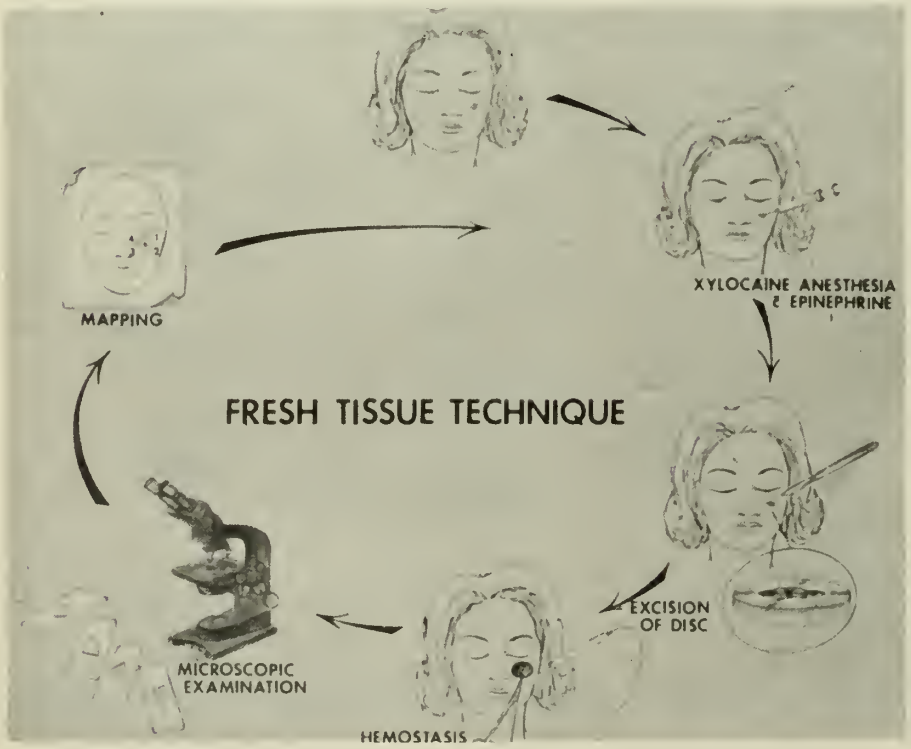

Figure 2.—The fresh tissue technique of chemosurgery. (Diagrams prepared by Philip Bailin, MD, Cleveland, Ohio.)

For large tumors, scalpel debulking is carried out first. The next step is to cut tissue sections so that the undersurface is flat or can be flattened out (Figure 3). Usually this means taking a thin 2- to 3-mm section of tissue in a cup-like shape from around the entire lateral surface and base of the freshly created defect (Figure 4).

The processing of the fresh tissues is then done in the same manner as the fixed tissues of classic chemosurgery. The tissues are divided into small pieces, carefully mapped and marked so that their orientation to the original location on the patient can be retraced and then are cut horizontally with a freezing microtome or cryostat starting on their undersurfaces. They are stained and ready for examination by the physician within 20 minutes to an hour. The physician studies the slides and, because they are horizontal sections, can identify residual tumor anywhere on the base or lateral surface of the wound. Any residual tumor is then diagrammed on the map; the physician reanesthetizes the patient if necessary and immediately takes further sections from only the involved areas. This same process for cutting, mapping, marking and processing frozen sections is repeated until the area is tumor free. The most important factor of the entire process is that the tissues are cut in such a way that they can be pressed flat so that the cryostat blade can cut the entire undersurface of the tissue.

The key factor of microscopically controlled excision which differentiates it from frozen sections taken vertically at random or in a series

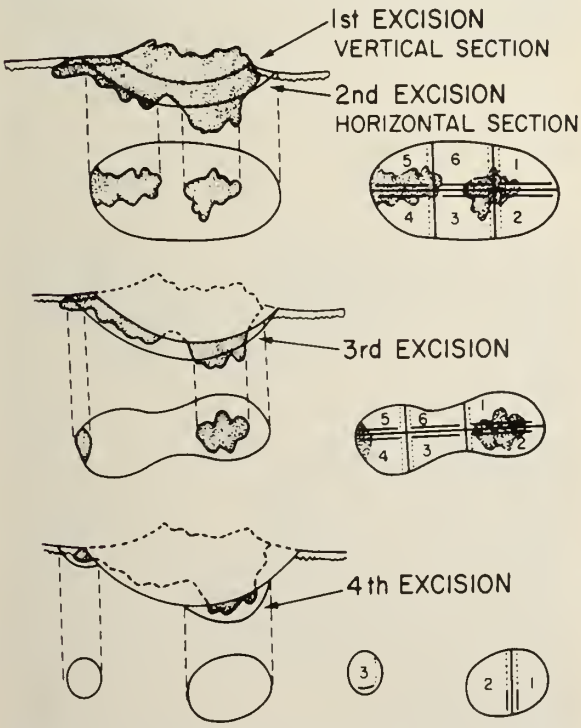

Figure 3.—Horizontal excisions of tissue in a cup-like fashion to obtain tissue specimens that can be flattened out on a cryostat objective holder and viewed in their entirety under the microscope after frozen sectioning. (Reproduced with permission from Mohs FE; Chemosurgery, Microscopically Controlled Surgery for Skin Cancer. Springfield, IL, Charles C Thomas, 1978, pg ix.)

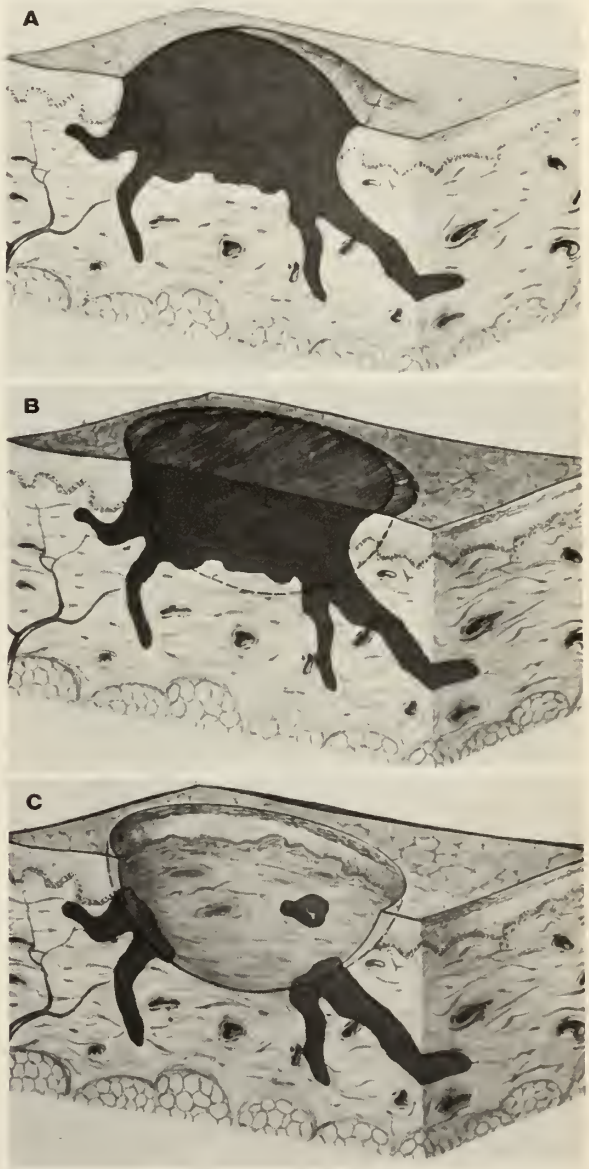

Figure 4.—Horizontal sectioning and microscopic examination of the complete lateral and undersurface of the cup-shaped excision is necessary to identify the small fibroepitheliomatous bands which often extend from a basal cell carcinoma. **A,** Tumor before excision. **B,** Tissue to be excised. **C,** Cup-shaped excision showing strands of tumor left behind after excision. (Drawings prepared by Philip Bailin, MD, Cleveland, Ohio.)

from tissues submitted for a routine surgical frozen section is that *no* portion of the wound margin is left unexamined (Figure 5). The horizontal sectioning allows microscopic inspection of the entire wound. Cure rate statistics support the contention that this technique gives a much higher cure rate for recurrent, difficult, or morphea basal cell epitheliomas than does standard surgical excision with frozen sections prepared in the usual manner and examined by random vertical sectioning.[1,2]

During the procedure hemostasis is obtained by the usual surgical methods: suture ligatures, electrodesiccation or electrocautery. A suction apparatus keeps the field free of blood. Most patients tolerate the procedure well, and in our experience preoperative sedation is not necessary. Sometimes three or even four excisions can be done in a single morning. Four excisions are adequate to eliminate about 90 percent of the tumors; however, some tumors are exceptionally large and require more cuts. Often, two cuts can be obtained under the same local anesthetic—the patient avoiding the pain of a second injection.

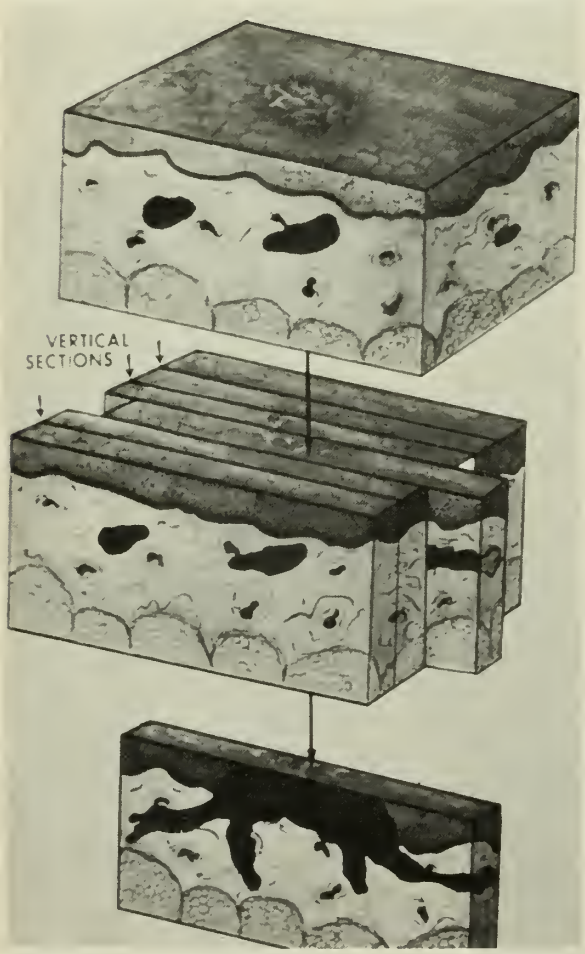

Figure 5.—Standard vertical sectioning of excised basal cell carcinomas often misses small fibroepitheliomatous tumors. It is often luck rather than control if the section examined by the pathologist contains one of the telltale strands. (Drawing prepared by Philip Bailin, MD, Cleveland, Ohio.)

There has been some confusion in the naming of this modification of Mohs' chemosurgery. Because the zinc chloride paste step has been eliminated from the procedure, it is erroneous to call the procedure *chemo*surgery. However, because of the recognition of the name there has been some attempt to keep that title. Physicians of all diciplines recognize that Mohs' chemosurgery indicates a surgical treatment to trace out difficult, large or involved skin tumors. Originally, the modification was called chemosurgery—fresh tissue technique. However, this title was altered to microscopically controlled excision (MCE). We are not entirely happy with this label but it is a useful and descriptive name. Dr. Walter Shelly has recently suggested that the procedure be called the MOHS technique using the Mohs not as an eponym but as a mnemonic for *m*icroscopically *o*riented *h*istographic *s*urgery.[8]

Advantages and Disadvantages

There are several advantages to the chemosurgery-modified method. First, the pain of using the zinc chloride paste is eliminated. The usual 24-hour paste fixation causes many patients much pain, sometimes requiring narcotics. If needed, the second pasting is applied to inflamed tissue, and the longer the procedure takes, the more painful it becomes. With MCE the prolonged pain of the paste is exchanged for the brief pain from the injection of a local anesthetic.

The modified method is also faster. The same amount of surgical treatment using MCE can now be accomplished in one or two days; formerly, the procedure required three to seven days. Most of the cases are completed within a single morning.

Another very important advantage is that once the borders of the wound are tumor free, the fresh wound can be closed by any number of standard surgical methods. On the contrary, the classic chemosurgery wound needs seven to ten days for the remaining fixed tissue to slough out. Then the patient must wait for healing by secondary intention or accept a split thickness graft. Thus, microscopically controlled excision is compatible with other surgical specialties. Ophthalmologists can request MCE of a tumor and then

can repair the defect themselves. The same is true for head and neck surgeons, otolaryngologists and plastic surgeons. This method is compatible with all of their work because the technique is strictly a cold steel surgical procedure.

The major disadvantage of the modified technique is one of adaptation. The treatment is surgical, requiring both surgical expertise and the ability to manage hemorrhage and open wounds. Because paste chemosurgery is nearly a bloodless procedure, often it can be done by the surgeon alone; however, the modified method requires both surgeon and well-trained assistants.

Another relative disadvantage is that because

Figure 6.—The scarred area along the nasal/facial groove of a patient in whom a recurrent basal cell epithelioma has been confirmed by biopsy. Previous treatment using the curettage and desiccation technique failed to excise the entire tumor.

Figure 8.—Morphea basal cell epithelioma confirmed by biopsy. The tumor has indistinct clinical margins and is cosmetically prominent on the nose of a very young patient.

Figure 7.—The extent of that tumor after extirpation with microscopically controlled excision. The tumor extended far wider and deeper than was clinically obvious.

Figure 9.—The final defect after microscopically controlled excision. The tumor extended wide in all directions and penetrated deeply between the lower lateral cartilages of the nose.

the wounds do not undergo a slough of the remaining fixed tissue followed by healing by secondary intention, there are, theoretically, two or three cell layers of tissue left in the patient that would have been sacrificed using the paste method. Conceivably, the two or three cell layers that are lost by the final paste sloughing and air desiccation of the wound healing by secondary intention might provide additional safety to insure that the tumor is completely ablated. Nevertheless, the cure rates of the modified method are comparable with the classic zinc chloride paste method.

Results

In an eight-year retrospective study (reported in part previously by the authors[7]) of 513 determinant cases of basal cell carcinoma treated with the modified method, there were eight recurrences, giving an overall cure rate of 98.4 percent. This compares favorably with the reported cure rates from zinc chloride paste chemosurgery. This retrospective study included 175 cases for which the follow-up was greater than five years; in this group the cure rate was 98.8 percent. Of the lesions, 22 percent were greater than 3 cm in diameter at the completion of the surgical procedure; 23 percent of the cases involved patients less than 50 years of age.

Of the eight recurrences, six were treated successfully with a second microscopically controlled excision. Two cases required other major surgical procedures for complete ablation.

Of the cases, 46 percent were primary tumors and 54 percent were recurrent tumors. Of the recurrent tumors, many had been previously treated with two or more of the standard modalities. In the eight years covered by the study there were several cases of squamous cell carcinoma treated with good cure rates; however, the numbers were too small to be significant.

Indications for Microscopically Controlled Excision

Any recurrent skin tumor deserves careful evaluation before retreatment because the cure rate for recurrent tumors with radiation therapy, curettage and desiccation or surgical excision falls in the range of 50 percent.[9,10] Whereas the cure rate for recurrent tumors by microscopically controlled excision usually exceeds 95 percent. It is generally assumed that a tumor that recurs after proper primary treatment is a type of tumor that is either eccentric or that has sent out small strands from the main tumor mass. For example, the scar of a basal cell carcinoma in the nasal facial groove area previously treated by curette and desiccation is shown in Figure 6. However, the full extent of the tumor invasion is dramatically shown in Figure 7 by the size of the defect produced after microscopically controlled excision.

Any morphea-type of basal cell carcinoma confirmed by biopsy should be considered for treatment primarily with MCE as the cure rate using other methods is lower. Figure 8 illustrates the indistinct clinical margins of a sclerosing type of basal cell carcinoma and Figure 9 depicts how large that tumor had actually grown in the deep dermal and subdermal layers. Tumors of long duration, greater than 2 cm in diameter, or tumors in the nasal/labial fold, the postauricular sulcus, the medial canthus or the external auditory canal all should be considered for treatment primarily with microscopically controlled excision. Any basal cell carcinoma or squamous cell carcinoma with indistinct clinical margins should also be considered as a relative indication for MCE.

The indications for MCE listed above do not conflict with the standard practice of treating well-defined basal cell carcinomas and squamous cell carcinomas with curettage and desiccation, radiation therapy or surgical excision. Cryotherapy is indicated in special instances and serves best in certain anatomic areas such as the lips or for superficial tumors on the trunk and extremities.

In very unusual cases, immunotherapy and chemotherapy may be considered.

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Refer to: Bouma DJ, Kammer H: Single daily dose methimazole treatment of hyperthyroidism. West J Med 132:13-15, Jan 1980

Single Daily Dose Methimazole Treatment of Hyperthyroidism

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The effectiveness of methimazole used in a single daily dose was studied in 47 patients during their initial episode of hyperthyroidism, and in an additional eight patients during a relapse of hyperthyroidism. All patients become euthyroid using this method. Mean time required to achieve a euthyroid state was 16.7±1.1 weeks in the former group, and 14.9±2.9 weeks in the latter. In one patient there was an initial response to single daily dose therapy, but subsequently split dosage was required for control. The single daily dose regimen of antithyroid drugs will control hyperthyroidism in most patients. We have found that propylthiouracil will achieve this more rapidly than methimazole.

METHIMAZOLE is an effective drug for treating hyperthyroidism. Most plans of therapy include administering the drug over a period of time in order to produce a lasting remission. In addition, it has been considered necessary to give medication at frequent intervals each day in order to gain control of hyperthyroidism. This, along with the protracted course of treatment, has detracted from the general acceptance of this form of therapy by patients and some physicians.

In recent years, it has been shown that most thyrotoxic patients can be treated effectively using single daily doses of propylthiouracil.[1,2] Not all practicing physicians, however, agree with this concept.[3] The purpose of this study is to investigate whether methimazole is also an effective antithyroid medication when given in single daily doses, thereby lending support to a simplified treatment plan. Some cases included herein are part of a previous report.[4]

Patients and Methods

All the patients in this series (Table 1) had hyperthyroidism due to diffuse toxic goiter. The patients were added to the study as they were referred for treatment and were not selected in any manner. These patients constituted 90 percent of thyrotoxic patients seen during this period; the remainder were treated with radioiodine at the request of the referring physicians. The radioiodine-treated group did not differ appreciably from the study group when age, sex, goiter size and hormone levels were considered. Several patients were seen at a time of clinical relapse, having previously taken propylthiouracil. None had ever received radioiodine therapy. Of the study group 50 patients were white and 5 were Asian (2 Chinese, 2 Japanese, 1 Vietnamese).

The severity of hyperthyroidism in 49 patients was categorized as shown in Table 2. In six additional patients there was triiodothyronine (T_3) toxicosis (greater than 50 percent elevation of T_3 levels only); three of these patients were considered to have mild and three to have moderate hyperthyroidism based on the criteria given in Table 2. The severity of ophthalmopathy in our patients as judged by American Thyroid Association standards[5] was as follows: 6 patients, class 0; 36, class 1; 6, class 2; 6, class 3, and 1, class 4. Radioiodine uptake studies were carried out in 38 patients (Table 3).

In all patients, therapy was begun with me-

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thimazole, 30 mg per day given in a single dose, and the patients were seen for follow-up examination at intervals of four to eight weeks. The dose remained unchanged as long as improvement occurred, based on clinical and laboratory data. If there was no improvement within the first two or three months of treatment, the drug dose was increased by an increment of 10 to 20 mg (see Table 4 for maximum dose employed). This was done at monthly intervals until improvement was noted. Patients were considered euthyroid when results of clinical examinations and thyroid function tests were normal.

Results

Therapy for Initial Episode of Hyperthyroidism

Of the 47 patients in this group, 46 became euthyroid when treated with single daily doses of methimazole. The average time required to achieve a euthyroid state was 16.7 ± 1.1 weeks (Table 5). Total length of continuous treatment ranged from six weeks to 33 months.

One patient whose condition was resistant to this form of therapy deserves special comment: A 16-year-old white girl with severe hyperthyroidism was treated with single daily doses of 30 mg of methimazole. After 26 weeks of therapy she became euthyroid and administration of the drug was discontinued. Hyperthyroidism recurred within three weeks and therapy with methimazole was begun again in the manner mentioned above. Because the hyperthyroidism had not improved after 24 weeks, she was asked to take her medication in a split dose regimen (10 mg every eight hours). She became euthyroid within eight weeks, and therapy with the drug was continued for an additional 35 weeks in an effort to produce a lasting remission. One month after the therapy was discontinued, thyrotoxicosis recurred. Once again she was treated with methimazole, 30 mg given as single daily doses. The hyperthyroidism was controlled with this regimen and the methimazole therapy was continued for an additional year. It was then discontinued and within three months a relapse occurred. At this point treatment with radioiodine was begun.

Therapy for Relapse of Hyperthyroidism

The eight patients in this group had received previous treatment for their hyperthyroidism and came under our care at a time of clinical relapse. Seven had been treated previously with propylthiouracil in a split dose regimen, and one had had a subtotal thyroidectomy. A euthyroid state was achieved in all with the use of methimazole, 30 mg given in a single daily dose regimen (Table 6).

Discussion

Any therapeutic program that can be simplified without losing effectiveness will increase patient compliance as well as acceptance by practicing physicians. A step in this direction came about when it was shown that many hyperthyroid patients can be managed successfully by administration of propylthiouracil in a single daily dose regimen.[1,2] Based on such experience it seemed likely that methimazole could be used in a similar

TABLE 1.—*Patients Treated with Single Daily Doses of Methimazole for Hyperthyroidism*

Age (years)	*Male*	*Female*
12-20	3	10
21-30	2	12
31-40	3	8
41-50	2	10
51-60	..	3
61-72	..	2
TOTALS	10	45

TABLE 2.—*Categories of Hyperthyroidism Severity in 49 Patients*

Mild (5 patients)
- Weight loss <10 pounds
- T_4 (adjusted) elevated <50 percent above upper limit of normal
- Estimated thyroid weight 20 to 40 grams

Moderate (33 patients)
- Weight loss 10 to 20 pounds
- T_4 (adjusted) elevated 50 percent to 100 percent above upper limit of normal
- Estimated thyroid weight 40 to 60 grams

Severe (11 patients)
- Weight loss >15 pounds
- T_4 (adjusted) elevated >100 percent above upper limit of normal
- Estimated thyroid weight 50 to 150 grams

T_4 = thyroxine

TABLE 3.—*24-Hour Radioiodine Uptake at Time of Diagnosis*

Percent Uptake	*Number of Patients*	*Percent Uptake*	*Number of Patients*
10-19	3*	40-49	7
20-29	7†	>50	11
30-39	10	Not done	17

*Nonsuppressible in 2
†Nonsuppressible in 4

fashion. Because both drugs are selectively concentrated by hyperthyroid tissue,[6] it would appear at first that neither holds a therapeutic advantage over the other. However, interference with iodine organification in the gland is more effective following methimazole administration. This increased effectiveness may be related to irreversible inhibition of thyroid peroxidase by methimazole in contrast to a reversible effect attributed to propylthiouracil.[7] Such activity leads to greater than 90 percent of inhibition of iodine 131 uptake 12 hours after administration of methimazole in hyperthyroid subjects as opposed to a 60 percent inhibition eight hours after a dose of propylthiouracil.[6] The known longer plasma half-life and greater whole body retention of methimazole[8] along with the above factor would tend to favor methimazole as the more effective antithyroid medication.

Barnes and Bledsoe[9] have shown the effectiveness of methimazole given in single daily doses. These authors were able to control hyperthyroidism in 77 percent of 44 patients when using a single daily dose of the drug, but were able to accomplish it in only 36 percent of 22 patients when propylthiouracil was used. They did not state how quickly euthyroidism was achieved using the different drugs. In our experience, euthyroidism was achieved in propylthiouracil-treated patients in an average of eight weeks,[2] whereas 16 weeks were required to achieve the same level of effectiveness in the methimazole-treated patients making up the present study. The ability of propylthiouracil to interfere with peripheral conversion of thyroxine to triiodothyronine may have been a factor. In general, the two groups of patients were comparable and the doses of medication used were of similar potency (assuming methimazole is ten times more potent by weight than propylthiouracil).

In our experience, in most hyperthyroid patients there is favorable response to antithyroid medication providing sufficient drug is given. Only occasionally will a case fail to improve using the single daily dose regimen. We have, therefore, not found it necessary to select suitable patients by pretreatment testing as suggested by Barnes and Bledsoe.[9]

The overall success of single daily dose regimens of antithyroid medications in management of hyperthyroid patients seems established. Both patients who have received previous treatment for thyrotoxicosis and those who have not may be treated in this fashion. This simplified plan does not lessen the necessity for the same precautions required when using antithyroid drugs in other manners. Careful patient evaluation at regular intervals is essential for successful treatment. Rapid control of hyperthyroidism may be accomplished more readily using propylthiouracil.

TABLE 4.—*Maximum Single Daily Dose of Methimazole in Treatment of Hyperthyroidism*

Number of Patients	*Mg of Methimazole*	*Number of Patients*	*Mg of Methimazole*
47	30	2	50
5	40	1	60

TABLE 5.—*Time Required to Achieve Euthyroidism with Single Daily Doses for Initial Episode of Hyperthyroidism*

Number of Patients	*Time to Euthyroidism (weeks)*	*Number of Patients*	*Time to Euthyroidism (weeks)*
8	5-8	3	21-24
7	9-12	5	25-28
10	13-16	2	29-32
11	17-20	1	33-40

Mean 16.7±1.1 weeks

TABLE 6.—*Time Required to Achieve Euthyroidism with Single Daily Doses for Relapse of Hyperthyroidism*

Number of Patients	*Time to Euthyroidism (weeks)*	*Number of Patients*	*Time to Euthyroidism (weeks)*
1	5-8	1	21-24
3	9-12	0	25-28
2	13-16	1	29-32
0	17-20	0	33-40

Mean 14.9±2.9 weeks

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The Clinical Physiology of Water Metabolism

Part III: The Water Depletion (Hyperosmolar) and Water Excess (Hyposmolar) Syndromes

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Hyperosmolality occurs when there are defects in the two major homeostatic mechanisms required for water balance—thirst and arginine vasopressin (AVP) release. In this situation hypotonic fluids are lost in substantial quantities causing depletion of both intracellular and extracellular fluid compartments. Patients with essential hypernatremia have defective osmotically stimulated AVP release and thirst but may have intact mechanisms for AVP release following hypovolemia. Hyperosmolality can also be seen in circumstances in which impermeable solutes are present in excessive quantities in extracellular fluid. Under these conditions there is cellular dehydration and the serum sodium may actually be reduced by water drawn out of cells along an osmotic gradient.

Hyposmolality and hyponatremia may be seen in a variety of clinical conditions. Salt depletion, states in which edema occurs and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may all produce severe dilution of body fluids resulting in serious neurologic disturbances. The differential diagnosis of these states is greatly facilitated by careful clinical assessment of extracellular fluid volume and by determination of urine sodium concentration. Treatment of the hyposmolar syndromes is contingent on the pathophysiology of the underlying disorder; hyponatremia due to salt depletion is treated with infusions of isotonic saline whereas mild hyponatremia in cirrhosis and ascites is best treated with water restriction. Severe symptomatic hyponatremia due to SIADH is treated with hypertonic saline therapy, sometimes in association with intravenous administration of furosemide. Less severe, chronic cases may be treated with dichlormethyltetracycline which blocks the action of AVP on the collecting duct.

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ABBREVIATIONS USED IN TEXT

ADH = antidiuretic hormone
AVP = arginine vasopressin
CNS = central nervous system
DI = diabetes insipidus
ECF = extracellular fluid
GFR = glomerular filtration rate
ICF = intracellular fluid
SIADH = inappropriate secretion of antidiuretic hormone

Hyperosmolar Syndromes

The circumstances in which the effective osmolality of body fluids is most likely to be increased above normal are a loss of water from the body in excess of sodium chloride (a hypotonic solution), the addition of a solute that does not freely penetrate cells, such as hypertonic glucose or mannitol, or a combination of both. (For details of these situations, see Table 12 in Part II.) In almost all instances in which there is a net hypotonic loss of water, hypernatremia occurs. Diabetes mellitus and prolonged administration of hypertonic mannitol solution are the only common clinical situations in which profound hypertonic dehydration may occur in the presence of normal or low serum sodium. In patients with uncontrolled diabetes accompanied by progressive hyperglycemia (and in patients receiving hypertonic mannitol), osmotic withdrawal of water from all body cells will cause severe cellular dehydration and dilution of the residual sodium in extracellular fluid (ECF). The extent of the lowering of plasma sodium by hyperglycemia per se can be estimated by multiplying 1.6 mEq per liter times each 100 mg per dl that the plasma glucose is elevated above normal. At times, however, especially in the syndrome of nonketotic hyperglycemic diabetic coma,[237] the magnitude of the water depletion may be so great that despite the profound hyperglycemia (greater than 1,000 mg per dl), which is so characteristic of this syndrome, the serum sodium will be normal or, more frequently, significantly elevated (greater than 145 mEq per liter).

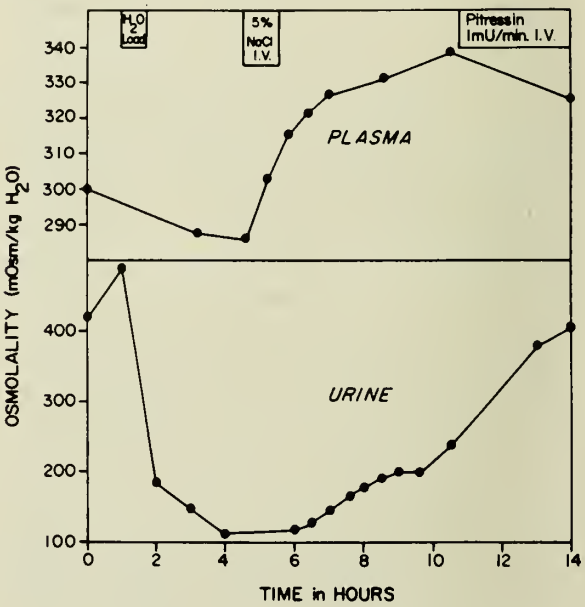
Investigators have become increasingly aware of the hypernatremic-hyperosmolar syndrome associated with hypertonic (glucose) peritoneal dialysis.[238] The latter (4.5 percent glucose added to the isotonic dialysis fluid) is commonly used to treat intractable edematous states, especially in association with severe renal failure. When this hypertonic solution is put into the peritoneal cavity, water moves along its osmotic gradient into the peritoneal cavity and extracellular electrolytes follow by diffusion. However, the glucose (4,500 mg per dl in the dialysis fluid) diffuses rapidly into the bloodstream, elevating blood glucose to values of 500 to 1,000 mg per dl. The pronounced extracellular hyperglycemia and hyperosmolality rapidly draw water out of all cells and dilute the salts of the ECF. The concentration of sodium in the blood and the ECF during this continuing unsteady state will fall below the sodium concentration in the dialysis fluid, thereby establishing a gradient for sodium and chloride to diffuse from the peritoneal cavity into the ECF. The net effect of this process at the end of the peritoneal dialysis is the removal of water in excess of isotonic proportions of sodium. When the hypertonic glucose in the ECF is metabolized by the patient, usually over 12 to 14 hours, the blood sugar returns to normal, the osmotic effect of the hyperglycemia disappears, water moves back into the dehydrated cells and the sodium and chloride concentrations in the blood and the ECF rise to hypernatremic levels. It is apparent that this hypernatremia will prevent the complete rehydration of all body cells. This whole syndrome can be prevented or minimized by using the least hypertonic dialysis fluid necessary to achieve the desired negative fluid balance, such as 1.5 percent alternating with 3 percent to 4 percent glucose, and by giving the patient adequate free water orally or parenterally to take care of all insensible and renal losses occurring during the dialysis.

Hypertonic dehydration is particularly prone to occur in elderly or unconscious patients who cannot respond to the thirst stimulus or who cannot adequately request water when it is needed. Furthermore, these persons are often tube fed a high-protein mixture or given parenteral hyperalimentation. Very often a large part of the administered protein or amino acids is not retained but is converted to urea, and the excretion of the latter causes a sustained osmotic diuresis. This, like any other osmotic diuresis, will produce large urinary volumes that are hypotonic with respect to sodium. The relatively high rate of urine flow falsely assures the physician that the patient is getting an adequate intake of fluid. In reality, a progressive contraction of body water is taking place. Peters referred to the pathophysiologic events accompanying profound water loss as the "rehydration reaction." This consists of a low urinary water

volume, a high urinary concentration and excretion of potassium, and, in spite of hypernatremia, a low concentration and excretion of urinary sodium.

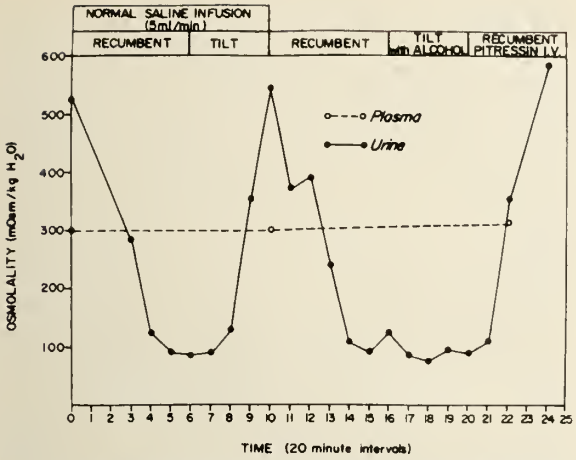
The unusual condition found in a group of patients of hypernatremia and hyperosmolality accompanied by supposedly normal hydration, and its differentiation from other sustained hyperosmolar states (see Table 12 in Part II), has been reviewed in detail by DeRubertis and associates.[38] They carefully investigated this syndrome in a patient in whom the condition had resulted from histiocytosis involvement of the hypothalamus. Abnormalities in water metabolism associated with lesions in this area appear to result from (1) impaired thirst, (2) impaired arginine vasopressin (AVP) production and secretion (diabetes insipidus) and (3) altered regulation of vasopressin secretion. These disturbances may occur either singly or in combination. DeRubertis has outlined the physiologic characteristics of those patients with hypernatremia and possibly normal hydration as follows. The sustained hypernatremia is usually not associated with a significant deficit of ECF volume as reflected by an absence of oliguria, azotemia or decreased urinary sodium content. The spontaneous fluid intake is generally low relative to the elevated plasma osmotic pressure, indicating defective thirst. In addition, the release of antidiuretic hormone (ADH) in response to osmotic stimuli appears impaired. However, endogenous ADH production is at least partially intact as implied by the concentration of urine under certain circumstances. In several of these patients hyperosmolality was not completely corrected by acute or chronic fluid loading, excluding inadequate fluid intake as the predominant factor in the disruption of osmotic homeostasis. It has been suggested that the sustained hyperosmolality in this group was the result of an elevated osmotic threshold for release of ADH. With such a disturbance in the osmotic regulation of ADH secretion, urine would be concentrated and water conserved only at very high levels of plasma osmolality. Thus, a new steady state at a high plasma osmolality would be maintained by this proposed upward "resetting of the hypothalamic osmostat."

This hypothesis for the cause of the hypernatremia appears to be supported in the patient studied by DeRubertis and associates. During 23 days of observation, in which the patient was receiving a normal diet and ad libitum water intake, plasma sodium fluctuated between 148 and 160 mEq per liter and plasma osmolality between 298 and 323 mOsm per liter. Endogenous AVP release was indicated by urine osmolalities as high as 710 mOsm per liter during water restriction, but only after a rise in plasma osmolality to 326 mOsm and a weight loss of 1.4 kg. Fluid intakes as high as 6 liters per day did not lower plasma osmolality, but merely led to a prompt water diuresis, indicating that simple water deficiency was not the cause of the hypernatremia. Hypertonic saline infusion during water diuresis, while causing a prounced increase in plasma osmolality, resulted



	U_1	U_2	U_3	U_4	U_5	U_6	U_7	U_8	U_9	U_{10}	U_{11}	U_{12}	U_{13}	U_{14}	U_{15}	U_{16}
Vml/min	1.0	0.8	2.9	2.5	2.4	2.7	16.5	18.3	11.9	4.5	11.5	8.2	5.1	8.3	3.4	6.3
C_{Osm}	1.4	1.3	1.8	1.3	1.0	1.0	6.4	8.3	6.0	2.4	6.7	5.0	3.1	5.9	3.8	7.6
C_{H_2O}	-0.4	-0.5	+1.1	+1.2	+1.4	+1.7	+10.1	+10.0	+5.9	+2.1	+4.8	+3.2	+2.1	+2.4	-0.4	-1.3

Figure 36.—Response to hypertonic saline infusion. After establishment of a water diuresis with an oral water load (H_2O load), 20 ml per kg of body weight, infusion of hypertonic saline (5 percent NaCl) given intravenously at 0.1 ml per kg of body weight per minute did not result in urinary concentration despite a pronounced acute rise in plasma osmolality (52 mOsm per kg of water, 18 percent in six hours). Rather, urinary (U) flow (maximum 18.3 ml per minute) increased with saline infusion. The maximum values were noted 90 minutes after cessation of the infusion. Water diuresis, still in progress at hour 10, was terminated with exogenous vasopressin (Pitressin, 1 mU per minute, given intravenously). Table, at bottom, depicts volume (V), osmolar clearance (C_{Osm}) and free water clearance (C_{H_2O}) in milliliters per minute, for individual determinations corresponding in sequence to points plotted for urine osmolality. (Reproduced with permission from DeRubertis FR, Michelis MF, Beck N, et al: J Clin Invest 50:97-111, 1971.)



	U_1	U_2	U_3	U_4	U_5	U_6	U_7	U_8	U_9	U_{10}	U_{11}	U_{12}	U_{13}	U_{14}	U_{15}	U_{16}	U_{17}	U_{18}	U_{19}	U_{20}	U_{21}	U_{22}
V ml/min	1.3	0.8	3.0	3.3	3.0	1.3	1.5	0.5	0.1	0.3	0.4	1.9	3.6	4.1	3.6	3.1	4.4	4.5	4.5	2.9	0.3	0.3
C_{Osm}	2.4	0.7	1.2	1.0	0.8	0.4	0.7	0.6	0.2	0.4	0.6	1.5	1.3	1.2	1.5	1.3	1.2	1.2	1.3	1.0	0.4	0.6
C_{H_2O}	-1.1	-0.1	-0.9	-2.2	-2.2	-1.1	-0.9	-0.1	-0.1	-0.1	-0.2	-0.4	-2.5	-2.9	-2.1	-3.8	-3.2	-3.3	-3.2	-1.9	-0.1	-0.3

Figure 37.—Interruption with orthostasis of a water diuresis induced by normal saline infusion. After overnight dehydration, a water diuresis was established during recumbency with normal saline infusion (5 ml per minute). Tilting to 75° for 90 minutes resulted in urinary concentration with urinary osmolality rising from 87 to 543 mOsm per kg of water. Water diuresis resumed with recumbency. Tilting was repeated 15 minutes after oral administration of ethanol-alcohol. Urinary concentration was not observed. During this study urine was collected at 20-minute intervals by an indwelling bladder catheter. Table, at bottom, depicts V, C_{Osm} and C_{H_2O} in milliliters per minute for individual determinations corresponding in sequence to points for urine osmolality. (Abbreviations the same as in Figure 36.) (Reproduced with permission from DeRubertis FR, Michelis MF, Beck N, et al: J Clin Invest 50:97-111, 1971.)

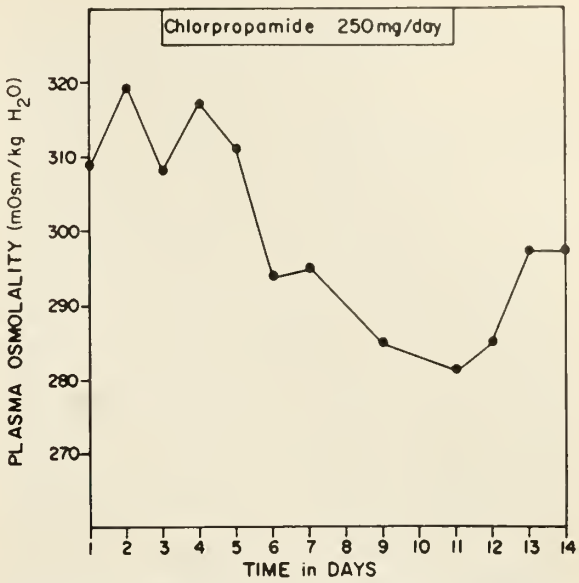


Figure 38.—Response to chlorpropamide. A significant fall in plasma osmolality (P_{Osm}) was noted on the fourth day of therapy with 250 mg of chlorpropamide per day. Response persisted for two days after cessation of the drug. Subsequent readministration of chlorpropamide resulted in a sustained lowering of P_{Osm}. (Reproduced with permission from DeRubertis FR, Michelis MF, Beck N, et al: J Clin Invest 50:97-111, 1971.)

in the excretion of an increased volume of hypotonic urine (Figure 36). An isotonic saline infusion, initiated during hydropenia, resulted in a water diuresis that continued despite a rise in the plasma osmolality from 302 to 320 mOsm per liter. The diuresis was terminated by orthostasis and resumed with return to the recumbent position (Figure 37). Antecedent alcohol ingestion blocked the antidiuresis of orthostasis (Figure 37).

These experimental observations indicate that the neurohypophysis was unresponsive to osmotic stimuli, but responded promptly and normally to nonosmotic volume changes of baroreceptor stimuli. In the steady state, the patient's extracellular volume (inulin space) was slightly below normal (11.2 liters with a predicted normal of 12), as was her blood volume of 3.3 liters with a standard normal of 3.7, corrected to height and lean body weight. DeRubertis suggested that the wide abnormal swings in random plasma osmolality (between 298 and 323 mOsm per liter) indicated that the altered AVP was not simply due to a resetting of the "osmostat," but was the consequence of (1) the loss of the sensitive osmotic regulation of AVP secretion, which normally maintains plasma osmolality at a relatively constant value, and (2) intact volume (baroreceptor) modulation of AVP secretion, which would result in relatively normal overall water balance but a less stable plasma osmolality.

The patient was given chlorpropamide orally in a dosage of 250 mg per day, which resulted in a return of plasma osmolality to a normal level after eight to ten days of therapy (Figure 38). Mahoney and Goodman[223] also successfully used chlorpropamide in a remarkably similar case of a patient with chronic hypernatremia. Bode and co-workers described a restoration of thirst with subsequent enhancement of oral water intake and amelioration of hypernatremia in patients with hypodipsia and diabetes insipidus (DI).[228] This effect on thirst suggests a possible central nervous system (CNS) site for action of chlorpropamide.

Chlorpropamide may be completely effective in this syndrome for two reasons, both based on its ability to substantially augment the presence of small amounts of AVP in the circulation. (1) A rise above normal in plasma osmotic pressure in

these patients may still have caused a minimal release of AVP into the circulation which, in the presence of the chlorpropamide, effectively increased water transport in the distal nephron, but in the drug's absence was ineffective. (2) Or, despite the complete absence of osmotic release of AVP in these patients, chlorpropamide so enhanced the action of minimal amounts of AVP in the circulation that the smallest volume deviations from normal were *adequate* to supply the minimal amount of hormone needed, given the presence of chlorpropamide, but *not adequate* in the drug's absence. These effects would complement any enhancement of thirst that might occur. The continued lethargy and clouded sensorium observed in these patients cleared completely when plasma sodium and osmolality returned to normal with therapy. DeRubertis and co-workers have subsequently described additional cases of essential hypernatremia.[239] In these cases and in others from the literature, there was evidence of *normovolemia,* intact nonosmolar secretion of AVP and defective osmolar stimulation of AVP. The absence of thirst seemed to play an important role in the pathogenesis of the hypernatremia. However, this could not be the entire explanation because oral water loading failed to correct the disorder. They pointed out that exogenous vasopressin returned levels of plasma sodium to normal, which suggested that AVP deficiency had a considerable role in the perpetuation of the hypernatremia.

It is not clear, however, whether such patients are truly normovolemic. Hypernatremia must be due to either a renal water loss in excess of water intake with normal total body sodium or to sodium excess. There is no evidence for the latter. Under conditions of water deficiency one would assume that both cellular and extracellular dehydration would be present and body fluid volumes reduced.

In recent years there have been several well-documented reports of hypernatremia in patients with severe plasma volume contraction.[240,241] These cases may represent a more extensive involvement of the hypothalamic-posterior pituitary system with simultaneous impairment of both osmolar and volume stimulation of thirst and AVP secretion. Urine volumes are kept normal because of renal and extrarenal factors that contribute to water retention in this condition. The low level of residual circulating AVP, when combined with (1) a decreased glomerular filtration rate (GFR) and renal blood flow, (2) enhanced reabsorption of solutes and water proximal to the collecting duct, (3) enhanced medullary tonicity over that observed in the nondehydrated state and (4) enhanced vasopressin-independent water reabsorption in the collecting duct as a consequence of the low rate of water flow through this segment, will result in the absence of polyuria as observed in these cases.

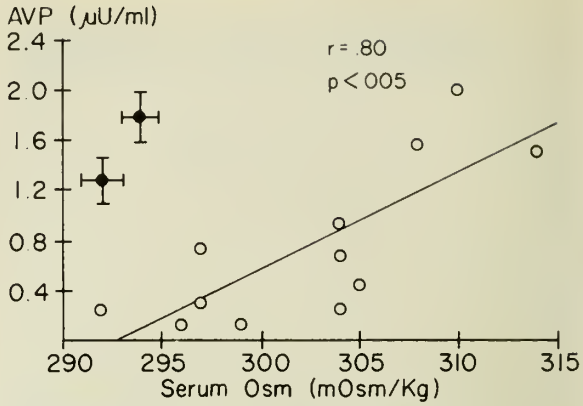


Figure 39.—Plasma arginine vasopressin (AVP) values plotted as a function of plasma osmolality in a patient with adipsia and hypernatremia (open circles). The mean values for plasma AVP and osmolality for 24 normal subjects after 12 and 18 hours of water deprivation (solid circles) are shown for comparison. Plasma AVP rose progressively with increasing plasma osmolality in this patient but always remains inappropriately low relative to plasma tonicity. Plasma AVP did eventually approach the normal range, but only at the expense of substantial hyperosmolality. (Replotted with permission from data of Grubb SR, et al: J Clin Res 25: 13A, 1977, and Weitzman R: unpublished data.)

Sridhar and colleagues[242] described a case of a 17-year-old girl who had originally had transient polydipsia and polyuria two years earlier and then presented with severe hyponatremia and hypovolemia unresponsive to oral water loading. When the urine to plasma (U/P) osmolar ratio was plotted as a function of serum sodium, it became apparent that the patient was capable of concentrating urine if the serum osmolality were sufficiently elevated. However, these investigators felt that the data did not support the concept of an elevated osmotic threshold for AVP release but, rather, suggested impaired AVP release at all levels of serum osmolality. A similar conclusion can be reached from the findings of Grubb and colleagues in their study of a unique case of a patient with adipsia following an episode of tuberculous meningitis in whom vasopressin-resistant hyposthenuria from streptomycin therapy also developed.[243] Levels of plasma

AVP were determined under varying conditions of hydration and were plotted as a function of plasma osmolality (Figure 39). In some instances, plasma AVP levels were well within normal range but this occurred only under circumstances of extreme hyperosmolality. As in the case described by Sridhar and associates,[242] there was considerable impairment of AVP secretion at all levels of plasma osmolality. In such patients, what little AVP release is observed after dehydration might be stimulated in part by relative hypovolemia.

Halter and co-workers[244] studied a case of chronic hypernatremia and hypodipsia in a patient, and found that although plasma AVP levels were inappropriately low for the given level of plasma osmolality, the patient was capable of substantially elevating plasma AVP after hypovolemic stimulation (Figure 40). As in the case described earlier, there was a significant correlation between plasma AVP and osmolality but with distinctly subnormal values for any degree of osmolality. The hypernatremia in these cases could be due to dysfunction of osmoreceptor stimulation of thirst and AVP release to spare magnocellular neurons for AVP synthesis. One might speculate that subsequent involvement of the supraoptic and paraventricular nuclei could eliminate even hypovolemic-stimulated AVP release which would result in deterioration of volume homeostasis, and profound hypovolemia. Thus, there may be a spectrum of disorders due to qualitative and quantitative defects in the separate components regulating thirst and AVP release (Table 13).

There is evidence for a functional and anatomic separation of the osmoreceptors for thirst from those for AVP release as well as from the neurosecretory neurons (see Figure 3 in Part I). It is possible to envisage a disease process selectively involving the magnocellular neurons in the hypothalamus or the axons traversing the pituitary stalk but sparing the thirst centers in the anterior hypothalamus. In this situation, renal water losses would produce hypertonicity of ECF which would, in turn, result in osmotically stimulated polydipsia and polyuria. The same clinical syndrome could also be produced by a disease process directly involving the osmoreceptors for AVP release but not those for stimulation of thirst. If the disease progressed further to impair the osmoregulation of thirst, polydipsia would cease and urine volumes would be reduced despite the continuing deficiency of AVP secretion. Renal water loss and impaired thirst would result in hypernatremia while nonosmolar stimulation of AVP would tend to minimize volume contraction. Finally, if the nonosmotic regulation of AVP secretion is impaired (probably by involvement of the magnocellular neurons themselves), then severe hypovolemia would ensue.

The proposed mechanism for hypernatremia associated with overhydration syndromes, such

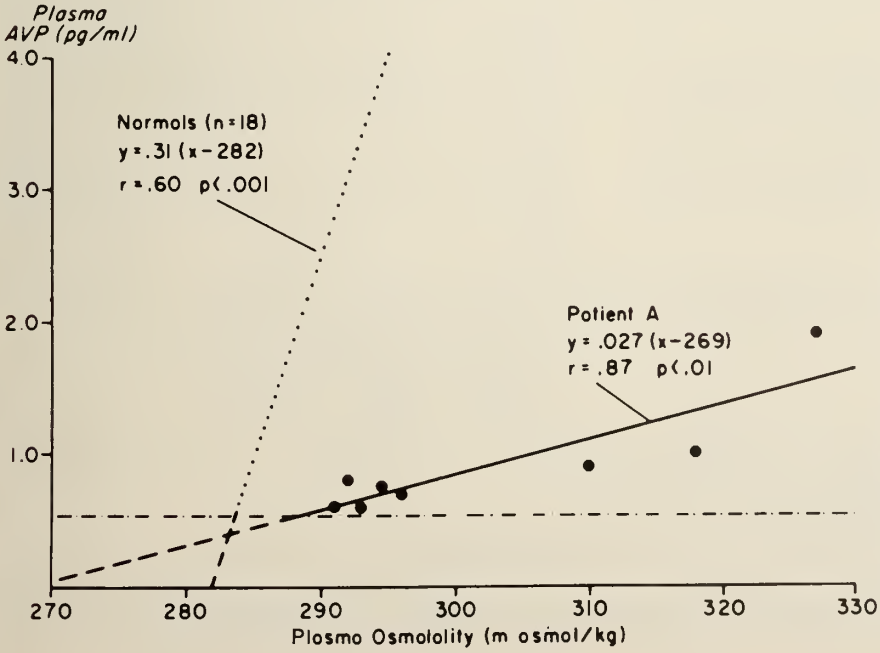


Figure 40.—Regression analysis of plasma arginine vasopressin (AVP) versus plasma osmolality (P_{Osm}) during hypertonic saline infusion in a patient with essential hypernatrema compared with the regression line for the plasma AVP-P_{Osm} relationship during hypertonic saline infusion in 18 normal subjects. The horizontal broken line represents the sensitivity limit of the plasma AVP assay (0.5 pg per ml). (Reproduced with permission from Halter JB, Goldberg AP, Robertson GL, et al: Selective osmoreceptor dysfunction in the syndrome of chronic hypernatremia. J Clin Endocr Metab 44:609, 1977.)

as primary hyperaldosteronism, was described earlier.

Clinical Manifestations of the Hyperosmolar Syndromes

If a patient is conscious, thirst may be extreme, unless there is a hypothalamic lesion causing defective thirst regulation. Severe hyperpnea may be present which does not resemble the deep, rapid breathing of Kussmaul respiration. Invariably there are significant alterations in the sensoria resulting in confusion, stupor and, eventually, coma. Almost any type of focal CNS neurologic syndrome may accompany the altered sensorium. Convulsions may occur rarely, and xanthochromatic or sanguineous spinal fluid may be found, confusing the diagnosis. The latter is due to a substantial increase in permeability or even rupture of the fine capillaries of the brain and subarachnoid space caused by the pronounced contraction of the brain, secondary to its osmotic water loss. Macaulay and Watson have shown that some children with no antecedent neural disorder but who survive from severe hypertonic dehydration, may be left with a state of generalized cerebral dysfunction characterized by impairment of intellect, clumsiness, hyperactivity and difficulty in social adjustment.[245] The most severe CNS dysfunctions are seen at both ends of the age spectrum and the more rapidly the hyperosmolality develops. Arieff and associates[246] have clearly shown that given time, the brain protects itself from dehydration by generating osmotically active substances ("idiogenic osmoles") which minimize the degree of water loss from the brain for any given increase in osmolality of the blood.

The skin and mucous membranes become extremely dry and usually erythematous. In contrast to dehydration associated with salt depletion, the actual skin turgor may remain fairly normal. However, hypotension, tachycardia and, at times, even hyperthermia without a discernible cause may be seen. Oliguria may be present, unless an osmotic diuresis is simultaneously occurring or a polyuric syndrome (see Table 12 in Part II) with hypotonic urine prevents renal water conservation. The concentration of hemoglobin and plasma proteins, as well as the hematocrit, will be elevated.

Water replacement using hypotonic solutions is the basic therapy of hyperosmolar states associated with water depletion. As the loss of water in this form of dehydration is derived proportionately from all fluid spaces, it is possible to calculate the magnitude of the deficit from the observed serum sodium concentration and the assumed normal total body water.[247] For example, an increment of 20 percent in the concentration of sodium (assuming no significant loss of total body solutes) will indicate a reduction of 20 percent in total body water. Therefore, the ratio of normal serum sodium over the observed serum sodium multiplied by the assumed normal body water (60 percent of the usual body weight) will approximate the total volume of free water to be replaced. This can be administered parenterally in the form of 2.5 percent to 5 percent glucose in water or hypotonic (75 mEq per liter) saline, in an amount calculated to return the serum osmolality to normal. Tap water can be taken orally, if possible, and tap-water enemas will be very rapidly absorbed from the rectosigmoid colon. However, it is critical not to correct the hyperosmolar state too rapidly. When rehydration and reexpansion of the brain are excessively rapid, convulsions and coma may ensue. An interval of 48 to 72 hours should be a reasonably safe period in which to return to an euosmolar state. The cause of the hypertonic dehydration should be corrected, if possible, and measures taken to avoid its occurrence. Any undiagnosed comatose,

TABLE 13.—*Development of Hypernatremia Owing to Progressive Disease of the Hypothalamic Centers for the Regulation of Thirst and AVP Release*

	*Polyuric Diabetes Insipidus**	*Normovolemic Hyper-natremia*	*Hypovolemic Hyper-natremia*
Osmolar regulation of AVP secretion	−	−	−
Thirst	+	−	−
Nonosmolar regulation of AVP secretion, (hypovolemia, hypotension or pressure)	+	+	−
Serum sodium	+↑	+↑	+↑

− = absent; + = present; ↑ = increased; AVP = arginine vasopressin.

*This syndrome could also be produced by selective destruction of the neurosecretory neurons or their axons in traversing the pituitary stalk, in which case nonosmolar stimulation of AVP secretion would be absent.

stuporous or confusional state in a child or adult who appears dehydrated should suggest this hypertonic dehydration syndrome.

Hyposmolar Syndromes

As water moves freely across all cell membranes along established concentration (osmolar) gradients, any lowering of ECF osmolality will result in an osmotic disequilibrium which, in turn, will produce a net flux of water from the ECF into the cells until osmotic equilibrium is reestablished. The resulting expansion of intracellular volume may alter cellular function and lead to definite symptoms. This is especially pronounced in the CNS where lethargy, seizures and coma may ensue.

In general, hyposmolality and hyponatremia are either synonymous or reflect each other. However, the presence of a lower than normal serum sodium concentration does not always imply the presence of hyposmolality. In patients having substantial elevations of either serum lipid or serum protein concentration, there is an artifactual reduction in the measured serum sodium concentration (Table 14). This is because the sodium is dissolved only in the water phase of the plasma. This phase normally amounts to 93 percent to 94 percent of a given unit of plasma volume. When there is a very large proportion of lipid or protein per milliliter, the water phase is proportionately reduced. Thus, while the concentration of sodium in *plasma water* appears normal, the concentration per milliliter or per liter of *plasma* is artifactually low. One can calculate the depression in measured serum sodium under these circumstances by multiplying the concentration of lipid in mg per dl by 0.002 or the elevation in serum protein concentration greater than 8 grams per dl by 0.25. In contrast, the osmolality or freezing-point depression of the plasma is not influenced by its fat or protein content. Therefore, osmolality can be correctly measured and the laboratory abnormality confirmed by finding a disproportionate reduction in sodium concentration relative to osmolality in the lipemic or substantially hyperproteinemic plasma.

A pathophysiologic situation in which hyponatremia is not associated with hyposmolality of ECF occurs when there are high concentrations of solutes of low molecular weight localized in the ECF compartment (Table 14). This can occur after intravenous infusion of large amounts of mannitol or glucose, or in patients with diabetes mellitus accompanied by severe hyperglycemia.

TABLE 14.—*Differential Diagnosis of Hyponatremia*

Hyponatremia category	Celluar dehydration	Artifactual	Hypovolemic	Minimal hypovolemic	Hypovolemic
Cause	Hyperglycemia, mannitol infused	Profound hyperlipidemia or hyperproteinemia	Salt depletion, third space	SIADH, myxedema	Cirrhosis, CHF, nephrosis
Status of ECF osmolality	Hyperosmolar hyponatremia	Euosmolar hyponatremia	Hyposmolar hyponatremia	Hyposmolar hyponatremia	Hyposmolar hyponatremia
ECF	↑ or ↓	Normal	↓	Normal or slightly ↑	↑
ICF	↓	Normal	↑	↑	↑
"Effective blood volume"	↑ or ↓	Normal	↓	Slightly ↑	↓
AVP	↑ or ↓*	Normal	↑†	↑†	↑†
PRA	Normal	Normal	↑	↓	↑
U_{Na^+}	Normal	Normal	↑ or ↓‡	↑	↓
Treatment					
Mild (symptomatic)	Treat underlying condition	Treat underlying condtion	Isotonic saline	Water restriction	Water restriction, treat underlying condition
Severe (symptomatic)	Treat underlying condition	Treat underlying condtion	Hypertonic saline	Hypertonic saline with furosemide, mannitol and dichlormethyltetracycline (Declomycin)	Hypertonic saline with furosemide

↑ = increased; ↓ = decreased; AVP = arginine vasopressin; CHF = congestive heart failure; ECF = extracellular fluid; ICF = intracellular fluid; PRA = plasma renin activity; U_{Na^+} = urinary sodium.

*Hyperglycemia produced by intravenous infusion of dextrose in water has been reported to lower plasma AVP while mannitol stimulates AVP secretion.
†AVP is elevated in relation to the concomitant level of plasma osmolality.
‡U_{Na^+} is low in extrarenal salt depletion and elevated in renal salt washing.

Under these conditions, the accumulation of osmoles in the ECF draws water from the cells which results in dilution of the sodium (in the serum or ECF). This type of hyponatremia has been designated cellular dehydration hyponatremia, and the magnitude of the depression of serum sodium can be calculated by multiplying the elevation in plasma glucose greater than 100 mg per dl by 0.016; that is, for every increase of 100 mg per dl in plasma glucose, the sodium will be diluted 1.6 mEq per liter.[248] Under most other conditions, hyponatremia signifies hyposmolality. This does not imply, however, that a single disease process or entity is responsible. The hyposmolar states can be further divided into three subcategories according to the status of the body sodium and water compartments (Table 14). The first category, which probably accounts for less than 30 percent of patients with hyponatremia, has been designated *hypovolemic hyponatremia or hypotonic dehydration.* In this condition there is a significant deficit of total body water, but there is an even larger deficit of total body sodium, the latter occurring by either renal or extrarenal routes. Clinically, the patients show signs of ECF volume depletion coexistent with expansion of intracellular fluid (ICF). Under these circumstances there is a pronounced reduction in ECF volume which, in turn, stimulates the renin-angiotensin system, thirst and the nonosmolar or volume activation of AVP release. This is combined with a reduction in GFR, enhanced tubular reabsorption of salt, and sodium and chloride concentration in the urine of usually less than 10 mEq per liter (unless the sodium loss occurred through the kidneys). The laboratory findings in this disorder are shown in Table 14 and Figure 41. This syndrome can sometimes occur in the absence of AVP, although AVP levels are frequently elevated in hypotonic dehydration. Earlier, we discussed the fact that moderately hypertonic urine and oliguria can be produced in the absence of AVP if the volume of salt and water delivered to the ultimate segments of the nephron is substantially reduced. In fact, in a severely sodium-depleted, congenital (Brattleboro) DI rat allowed free access to water, a degree of hyponatremia and oliguria may develop that is almost indistinguishable from that of a salt-depleted non-DI rat allowed free access to water (Figure 42).[249]

The second category probably accounts for at least 60 percent of patients with hyponatremia in hospitals. It is due, basically, to a primary excess of total body water associated with a nor-

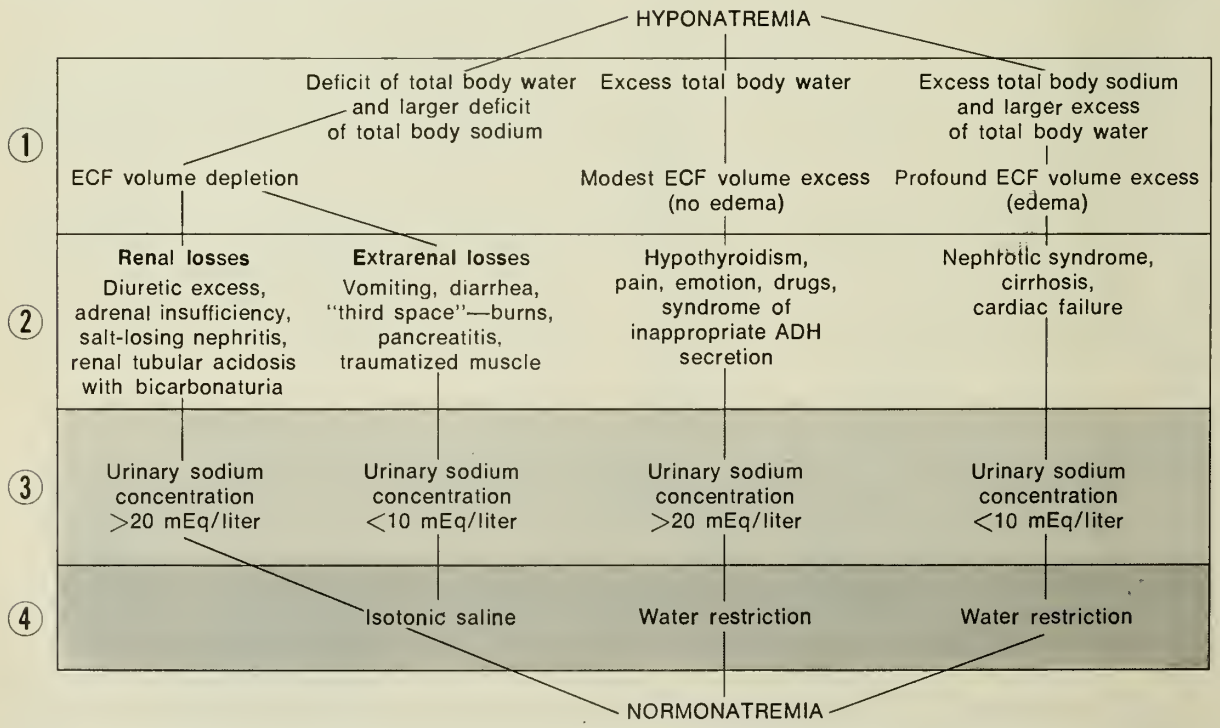


Figure 41.—Diagnostic and therapeutic approach to hyponatremia. ECF = extracellular fluid. (Reprinted with permission from Schrier R, Berl T: Disorders of water metabolism, *In* Schrier RW (Ed): Renal and Electrolyte Disorders, Boston, Little, Brown & Co, 1976, p 36.)

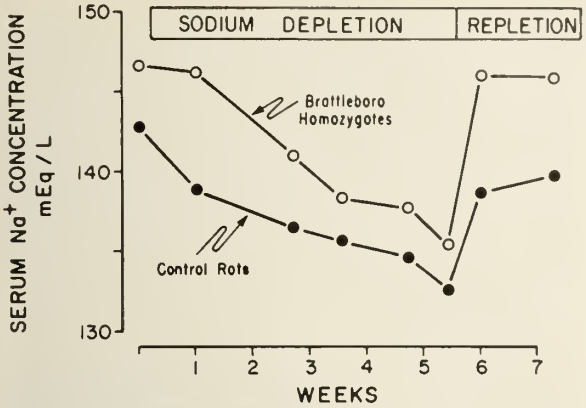


Figure 42.—Development of hyponatremia during NaCl depletion in seven control rats and eight Brattleboro homozygotes. Similarity of responses suggests that vasopressin is not required for selective retention of water seen during sodium depletion. (Data from Harrington AR: Am J Physiol 222:768, 1972. Reproduced with permission from: Valtin J, et al: Recent Progress in Hormone Research 31:466, 1975.)

mal or slightly decreased total body sodium. This condition has been designated *hyponatremia with minimal hypervolemia.* Under these conditions there is an across-the-board expansion of intravascular, interstitial and ICF compartments proportional to their relative sizes; that is, each compartment is increased by the same fractional amount. These patients have a primary defect in the renal excretion of free water. The clinical and laboratory characteristics of these patients are described in Table 14 and Figure 41.

Excluding patients with chronic renal failure, in whom impaired water excretion may result simply from a substantial reduction in renal mass,[250] there remain those patients in whom water excretion is inadequate despite a structurally intact kidney. This failure could be due to (1) an alteration in renal function, which prevents the delivery of an adequate volume of water to the diluting segments of the nephron (ascending limb of the loop of Henle, distal convoluted and collecting tubules) (Table 15); (2) an abnormal permeability of these segments to water despite the absence of circulating ADH (arginine vasopressin), or a substance such as oxytocin which in high concentration can mimic the effect of AVP on the nephron; such an abnormal permeability *may* be present in patients or animals with a deficiency of adrenal glucocorticoids, such as cortisol, or (3) a sustained level of circulating AVP which causes an increased permeability to water of the distal convoluted tubule and collecting duct.

Each of these conditions could make the urine more concentrated and lower in volume than is *appropriate for a given solute and water intake,* thereby resulting in abnormal water retention and hyposmolality of body fluids. While the second condition described above may be confined to adrenal cortical insufficiency,[251] the first and third conditions may frequently be present together and result in a greater impairment in water excretion than in either circumstance alone.[250,252] In fact, at

TABLE 15.—*Physiologic and Pathologic Factors Altering Maximal Water Diuresis and Urinary Dilution Independent of AVP*

Rigid sodium restriction or sodium depletion impairs water diuresis
- Decreased filtered load of sodium and water
- Enhanced proximal tubular reabsorption of sodium and water
- Decreased delivery of sodium and water to distal tubule
- Decreased velocity of flow to loop of Henle
- Decreased medullary blood flow

Glomerular filtration rate
- Decreased GFR may impair maximal water diuresis by above mechanisms; increased GFR does the reverse

Medullary blood flow
- Decreased medullary blood flow impairs maximal water diuresis by increasing hypertonicity of medulla which allows increased back diffusion of water in descending limb and collecting duct in absence of AVP; increased medullary blood does the reverse

Osmotic diuresis
- Increases water diuresis (free water clearance) but causes an increase (less dilute) in minimal urinary osmolality because of increased delivery of solute and water to diluting segments

Diuretics
- Impair maximal urinary dilution and water diuresis:
  - Induce sodium depletion with resultant changes
  - Selectively block sodium resorption by the cortical diluting segment (thiazides) or in the ascending limb (furosemide, ethacrynic acid, ? mercurials) as well

Chronic renal failure
- Impairs maximal diuresis and urinary dilution by:
  - Decrease in number of functioning nephrons
  - Increase in osmotic load per nephron

Primary or secondary adrenal glucocorticoid deficiency
- Impairs maximal water diuresis and urinary dilution:
  - Decrease in GFR and (?) medullary blood flow
  - Enhancement of back diffusion of water in the diluting segments of the nephron in absence of AVP
  - Inappropriate secretion of AVP on basis of volume depletion or ? stress

Hypothyroidism
- Impairs water diuresis by:
  - Decrease in GFR and (?) renal medullary blood flow
  - (?) Inappropriate secretion of AVP

Prostaglandin "deficiency"
- Administration of PGE synthetase inhibitors such as indomethacin

AVP = arginine vasopresssin; GFR = glomerular filtration rate; PGE = prostaglandin E.

times all three situations may contribute to the defect in water excretion almost invariably present in primary or secondary adrenal insufficiency.[250,251] The abnormalities in renal function mentioned could prevent a *necessary* water diuresis, the urine being relatively low in volume and *less* hypotonic than it should be—perhaps, being even moderately hypertonic. Confronted with this situation, one might be unable to determine whether the impaired diuresis is the result of an *inappropriate* circulating level of AVP or some other antidiuretic material, an altered renal function or a combination of both. Bartter and Schwartz, in their original review of hyposmolar syndromes,[252] stressed the importance of a critical evaluation of the nonhormonal factors presented previously and the need for a more specific identification of the antidiuretic activity detected in the biologic fluids of certain of these patients.

Appropriate and Inappropriate Release of AVP

The known regulators of AVP secretion were discussed earlier (see Table 3 in Part I) and, at this point, it is necessary to clarify the meaning of the term *inappropriate*. The final common pathway is made up of the nerve cell bodies of the hypothalamic supraoptic nuclei, and the rate of hormone release at any moment will be the algebraic sum of its stimulatory and inhibitory impulses. We have stressed the continuous delicate balance that exists between osmotic and nonosmotic (such as baroreceptor, chemoreceptor and thermoreceptor) stimuli impinging on this final common pathway. We know that normally a positive water balance, with its consequent drop in the osmolality of blood perfusing the hypothalamic osmoreceptors, will inhibit the release of AVP to a degree necessary to establish normal water diuresis (see Table 7 in Part II). As mentioned earlier, small amounts of AVP may continue to be released into the circulation at this time owing to the tonic stimulation of the nonosmotic baroreceptors (see Table 3 in Part I). However, if a significant fall in blood pressure or cardiac output, a decrease or redistribution of blood volume or a combination of both causes a sustained change in impulses from these receptors, AVP release will be maintained at a higher level despite the positive water balance, and the necessary water diuresis will not occur.

Table 16 distinguishes between *appropriate* release of ADH in response to nonosmotic stimuli and the truly *inappropriate* release of antidiuretic peptides, whether derived from the neurohypophysis or from an ectopic source such as a malignant tumor that is producing AVP. It is important to emphasize that the states listed in Table 16 which also lead to hyponatremia are the same as those in which functional alterations in renal hemodynamics and the renal handling of solutes and water may impair water diuresis *in the absence of any circulating antidiuretic material.*

The sustained release of AVP in these syndromes

TABLE 16.—*Clinical Hyposmolar States Associated With Measured or Probable Increased Secretion of ADH*

States in which ADH may be released (appropriately) in response to the nonosmotic stimuli: Decreased arterial pressure (? pulse pressure) in carotid and, possibly, aortic baroreceptors; decrease in tension in the left atrial wall and great pulmonary veins.

Hypovolemia, hypotension and decreased cardiac output secondary to blood loss or loss of extracellular volume of any cause

Intrinsic myocardial disease of any cause with reduced cardiac output of acute or chronic nature, edematous states with hyponatremia (enhanced proximal tubular resorption of salt and water may at times be more important than increased ADH secretion in the impaired water excretion)

- Cirrhosis with ascites or after large paracentesis*
- Nephrotic syndrome with hypoalbuminemia and hypovolemia
- Congestive heart failure
- Postmural valvulotomy, with (?) relief of distention of left atrial receptors (Table 3)*

States in which ADH secretion may be increased despite the absence of appropriate stimuli (Table 3) ("inappropriate" ADH syndrome): Bronchogenic carcinoma,* adenocarcinoma of the pancreas,* lymphosarcoma, duodenal adenocarcinoma,* pulmonary tuberculosis, pulmonary abscess,* subdural hematoma,* brain tumors,* subarachnoid hemorrhage,* cerebral vascular thrombosis,* skull fractures,* cerebral atrophy,* central pontine myelinolysis,* paroxysmal seizure disorders, acute psychoses,* herpes simplex encephalitis, administration of large quantities of oxytocin and water to obstetric patients, Guillain-Barré syndrome, tuberculosis meningitis, purulent meningitis, acute intermittent porphyria,* myxedema,* postoperative ADH release due to morphine, barbiturates,* cyclophosphamide, vincristine,* carbamazepine,* anesthesia or surgical stress,* transient "idiopathic" hyponatremia (secondary to diuretics, especially thiazides*), and ADH release after surgical procedures* and after hypophysectomy.*

Hyponatremic states with absolute or relative overhydration in which factors other than sustained inappropriate ADH secretion may be responsible for impaired water excretion

Primary and secondary adrenal (glucocorticoid) insufficiency

Chlorpropamide* and, rarely, tolbutamide ingestion

ADH = antidiuretic hormone

*Increased levels of ADH have been measured in serum, urine or tumor extracts by bioassay or immunoassay.

is due to one or more of the following: (1) An abnormal stimulation, by CNS dysfunction or disease, pain, drugs, or psychosis (see Table 3 in Part I), of those areas of the reticular formation, limbic system or cerebral cortex which have neural connections with the hypothalamic, supraoptic and paraventricular nuclei; (2) the stimulation of the nonosmotic mechanisms as listed in Table 3 (see Part I) or (3) tumors of varied causes that have been observed by analysis of the tumor, plasma or urine to contain an antidiuretic material biologically indistinguishable from AVP (Table 16). Those disorders in which AVP is secreted independently of known osmotic or nonosmotic pathways, as described in the first and third conditions above, are called syndromes of inappropriate secretion of ADH (SIADH).

In Table 16, asterisks designate those clinical states in which antidiuretic activity has been detected in plasma, urine or tissue extracts by bioassay,[253] radioimmunoassay, or both.[245,253,254] (Some of these studies have been reviewed by Bartter and Schwartz.[252]) Table 17 presents findings in patients with neoplastic disease and SIADH.[253] In five of the patients, significant quantities of antidiuretic material were extracted from the original tumor or its metastases. This material was identified as arginine vasopressin by immunoassay in four, and by complete inactivation of the antidiuretic activity by human pregnancy plasma (vasopressinase) and rabbit vasopressin antisera in all five. Although the concentration of AVP per milligram of dried powder (47 to 763 units) is only a fraction of that in the human neurohy-

TABLE 17.—*Characteristics of Tissue, Plasma and Tumor Antidiuretic Principle From Patients With Inappropriate ADH Syndrome**

	Antidiuretic Activity μU/mg Powder				*Milk-Ejection Activity μU/mg Powder*	
			After Incubation			*After Incubation*
Specimen	*Bioassay*	*Immunoassay*	*HPP*	*VAR*		*VAR*
• Bronchogenic carcinoma	763±53†	610	ϕ	ϕ	169± 7	ϕ
Normal lung	ϕ				ϕ	
• Bronchogenic carcinoma	162±13	116	ϕ	ϕ	58± 8	ϕ
Hepatic metastasis	ϕ	10			ϕ	
Normal lung	ϕ	<3			ϕ	
Normal liver	ϕ	<4			ϕ	
Plasma	15/ml		ϕ			
• Bronchogenic carcinoma	150±14		ϕ	ϕ		
Liver metastasis	ϕ	<4				
Plasma	ϕ					
• Bronchogenic carcinoma	130±10		ϕ	ϕ	ϕ	
Breast metastasis	740±76	1,540	ϕ	ϕ	124±11	ϕ
Mediastinal metastasis	283±19	120	ϕ	ϕ	48± 2	ϕ
Brain metastasis	307±72		ϕ	ϕ		
Kidney metastasis	ϕ				ϕ	
Normal lung	ϕ				ϕ	
• Adenocarcinoma of pancreas	ϕ				ϕ	
Hepatic metastasis	47± 7	24	ϕ	ϕ	ϕ	
Plasma	8/ml					
• Bronchogenic carcinoma	ϕ	<20			ϕ	
Hepatic metastasis	ϕ	<1			ϕ	
Normal lung	ϕ	<5			ϕ	
Normal liver	ϕ	<3			ϕ	
• Bronchogenic carcinoma						
Biopsy	ϕ				ϕ	
Autopsy	ϕ				ϕ	
Plasma	ϕ				ϕ	
• Bronchogenic carcinoma	ϕ	<4			ϕ	
• Bronchogenic carcinoma	ϕ	<4			ϕ	
Plasma	10/ml		ϕ			
• Bronchogenic carcinoma	ϕ	<5			ϕ	

HPP = human pregnancy plasma, VAR = vasopressin antiserum from rabbit, ϕ = < 10-20 μU/mg powder for vasopressin and < 12.5-25 μU/mg powder for oxytocin.

*Reprinted with permission from Vorherr et al.[253]
†Mean values ± standard error were calculated from values obtained in three to five rats. For each rat the average of several assays was used.

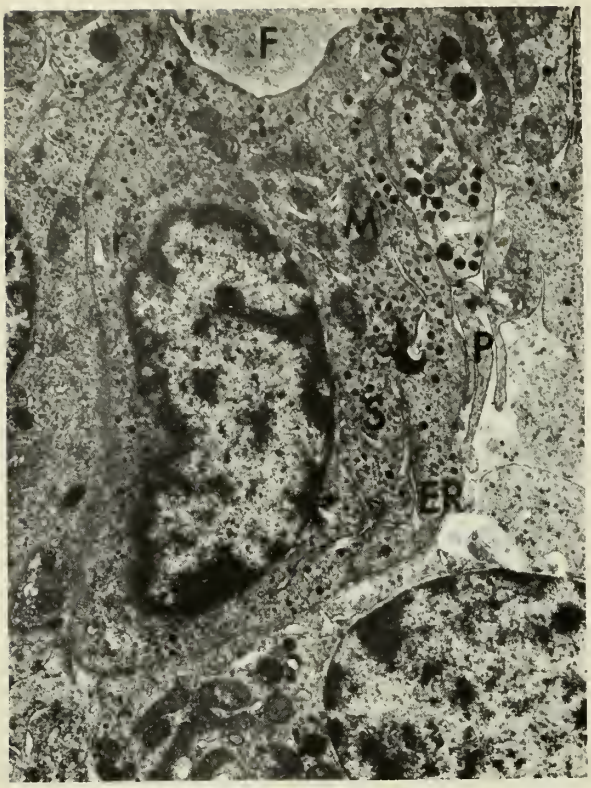


Figure 43.—Neoplastic cell with numerous intracytoplasmic secretory granules (S) and long profiles of endoplasmic reticulum (ER) with attached ribosomes. These cells were observed less frequently than the poorly differentiated neoplastic cells (at left and bottom). In addition to the secretion granules, large mitochondria (M) and aggregations of free ribosomes (r) were present in the cytoplasm. Cytoplasmic projections (P) extended into the prominent intracellular spaces which often contained a network of intermeshed fibrils (F) (reduced from ×11,300). (Reproduced with permission from George JM, et al.[255])

pophysis (85 mU per mg of dried powder), the total mass of the tumor is so great that it is capable of releasing enough hormone to cause a sustained inappropriate AVP syndrome. It should be emphasized that in five patients (Table 17), despite the classic hyposmolar syndrome, no antidiuretic activity was detected in their tumors. Either the syndrome in these cases was due to sustained nonosmotic release of AVP from the neurohypophysis, or the concentration of the hormone in the tumor at the time of extraction was too low to be detected by the assay procedures.

The presence of AVP in tumor extracts, blood and urine, although strongly suggestive that the tumor is the source of the inappropriate AVP *secretion,* is not final proof. The latter requires verification that the tumor is actually capable of producing the hormone. This has been achieved by George and co-workers.[255] They studied an extract of bronchogenic carcinoma that had been removed from a patient with the classic syndrome of inappropriate secretion of AVP and found 23.5 mU of vasopressin per gram of wet weight by radioimmunoassay. Slices of the tumor were incubated with phenylalanine-3H and arginine-vasopressin-3H was purified from the incubate, thus showing in vitro biosynthesis of vasopressin by the tumor. On electron microscopy the small undifferentiated cells of the tumor had well-developed endoplasmic reticulum and ribosomes. Secretion granules surrounded by limiting membranes were present which resembled those seen in polypeptide hormone-secreting cells (Figure 43). Vorherr[256] has recently added additional proof that malignant tumors can be the source of the AVP.

Chronic pulmonary tuberculosis was one of the earliest described causes of the hyposmolar syndrome referred to as "pulmonary salt wasting."[252] Vorherr and associates[257] have clearly shown the presence of vasopressin in tubercular lung tissue from a patient with advanced pulmonary tuberculosis and a typical syndrome of inappropriate secretion of AVP. The extracted tissue contained 22 units of vasopressin per milligram of dried extract. The uninvolved lung tissue, the suspension of *Mycobacterium tuberculosis* and the culture with its metabolites failed to show antidiuretic activity. This is the first case in which a relationship between AVP and hyponatremia in a patient with pulmonary tuberculosis has been shown. Pulmonary diseases of other etiologies have been associated with SIADH. These include chronic obstructive pulmonary disease with emphysema, acute lobar pneumonia and empyema. In some of these syndromes it has been suggested that AVP release might be provoked by impaired pulmonary compliance and some diminished stretch of the great pulmonary vein or left atrial receptors.

Pathophysiology of Water Retention in Minimal Hypervolemic Hyponatremia

The hyposmolar syndromes may or may not be associated with overt edema or reduction in the renal hemodynamics, neither of which is essential to the development of the water retention and hyposmolar state. The mechanism in the nonedematous cases is identical to that which results from the continuous administration of exogenous vasopressin (Pitressin) to normal subjects ingest-

ing a constant and liberal amount of water (Figure 44).[258] The patients are found to have hyponatremia, hypochloremia, normal or low blood urea and creatinine (unless a separate cause for renal impairement exists), mild to moderate oliguria, and a urinary excretion of sodium in excess of 25 mEq per 24 hours, or approximating intake. Note that although the dose of vasopressin was constant throughout the experiment with the normal subjects, urinary osmolality and oliguria were considerably greater in the first few days of its administration (Figure 44). Subsequently, urine volume rose and the concentration of the urine, although still hypertonic, approached the pre-Pitressin period. This *escape* from the maximal renal effect of the hormone must be related to the intrarenal and extrarenal response to the progressive expansion of total body water. It is referred to by Bartter and Schwartz[252] as a new "steady state" in which the degree of hyposmolality or hyponatremia may range from slight to as low as 100 to 110 mEq per liter. During this period urinary sodium usually reflects intake. Although it is evident that the new steady state protects the patient from even more severe degrees of oliguria and water retention, the hyposmolar syndrome will persist as long as a normal water diuresis cannot occur or the patient remains in positive water balance.

Rigid restriction of water (negative water balance) returns the serum sodium level to normal in association with a prompt and substantial reduction in sodium excretion (Figure 44). The cause of the relatively high urinary sodium or the sodium loss has been attributed in part to hypervolemic inhibition of aldosterone secretion in association with an actual increase in the GFR and the filtered load of sodium.[252] However, in some patients urinary aldosterone excretion and GFR have been within normal range despite the continued urinary loss of sodium, indicating that some additional mechanism must be present.[117,118] Fichman and co-workers have reported that although plasma renin activity is considerably suppressed in cases of SIADH or after administration of Pitressin, plasma aldosterone levels are normal and fully responsive to endogenous and exogenous stimuli. It would appear that the most reasonable explanation for the enhanced loss of sodium in SIADH is that the increased total body fluid with expansion of the plasma and extracellular volume causes an inhibition of tubular reabsorption of sodium which may cause enhanced excretion of sodium despite continued secretion of aldosterone.[117,118]

Nolph and Schrier[259] carried out a careful and accurate balance study on a patient with cerebrovascular disease and a syndrome of inappropriate

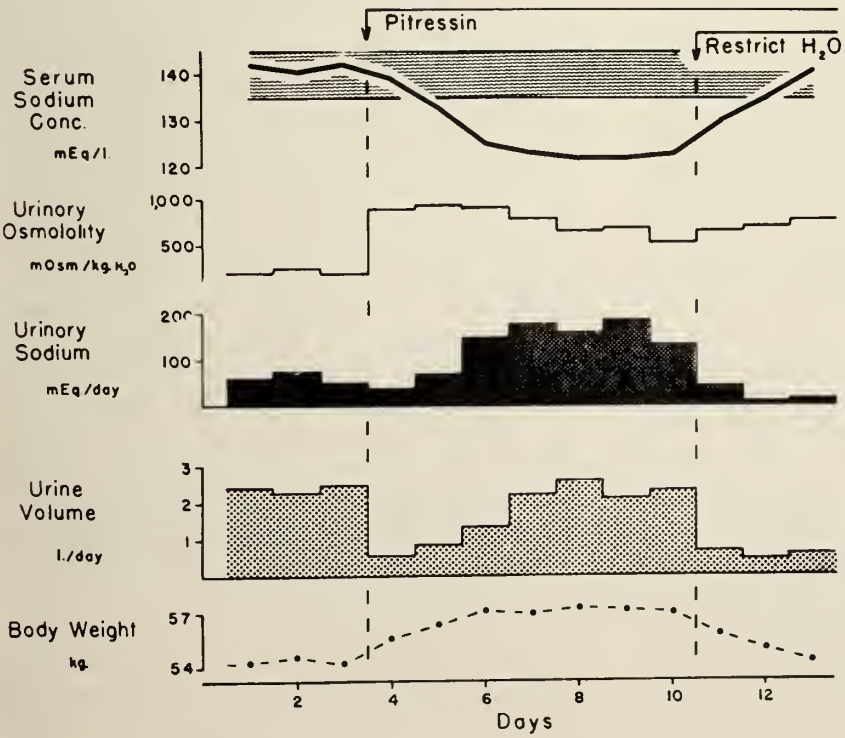


Figure 44.—Diagrammatic summary of the effects of Pitressin and water administration to normal subjects. (Reproduced with permission from Goldberg M: Med Clin N Amer 47:915, 1963.)

secretion of AVP. The results of their study are most helpful in explaining some of the unusual biochemical features of the syndrome. Weight gain and decreased plasma sodium always occurred when the daily fluid intake was 25 ml per kg, causing a gradual expansion of body fluids; 30 ml per kg led to a rapid expansion. The latter caused a sudden increase in sodium excretion, whereas the gradual expansion resulted in minimal, if any, increase in sodium excretion. Aldosterone excretion rates were normal during the control and volume expansion periods. The authors concluded that negative sodium balance, owing to renal loss of sodium, did not contribute substantially to the hyponatremia with either gradual or rapid expansion. During both states, estimated net positive water balance greatly exceeded the actual weight gain. We have observed this phenomenon as well. Because the patient was receiving an isocaloric diet throughout the study, the results suggest that the positive water balance in this syndrome may enhance pulmonary and cutaneous insensible water loss so that more water is retained by balance than is actually calculated from weight gain. During water restriction and recovery from hyponatremia, sodium excretion was well below the control level. This was associated with a rapid return of the plasma sodium concentration to normal over several days with *only slight weight loss relative to the weight gain* that occurred during the previous water expansion period. Aldosterone excretion increased during the recovery period and, together with increased proximal resorption, may have been responsible for the positive sodium balance. During a period of gradual expansion (fluid intake 25 ml per kg), if the patient's intake of sodium was high, isonatremic volume expansion occurred. Positive sodium balance protected against the development of hyponatremia. Thus, an inappropriate retention of water can occur in this syndrome *without* the development of hyponatremia if the rate of fluid ingested is not too great and if the patient's intake of sodium is relatively high.

It should be stressed that for a water intoxication syndrome to develop, there must only be an inability to achieve a water diuresis when hyposmolality of the body fluids exists. Although hypertonic urine is frequently present, a patient may be excreting isotonic or even slightly hypotonic (200 to 250 mOsm per liter) urine. At this point acute expansion of the ECF with *isotonic* saline (which is actually hypertonic to the patient) may paradoxically cause a mild water diuresis, with the urine becoming even more hypotonic. This has been observed when the inappropriate secretion of AVP is due to a bronchogenic carcinoma.[252] If the latter is secreting AVP, it is unlikely that volume expansion would inhibit the release of the hormone from the tumor. Therefore, the paradoxical water diuresis is probably due to a renal "escape" from the antidiuretic effect. As mentioned by Bartter and Schwartz, "an analogous 'escape' is seen in normal dogs given infusions of saline and vasopressin and has been attributed to an increase in tubular flow of a magnitude such that there is inadequate time for osmotic equilibration in the distal portion of the nephron."[252]

At times, however, when a sustained nonosmotic release of AVP from the neurohypophysis is the cause of the hyposmolar syndrome, the patient may respond to the water load with a normal water diuresis. This suggests that the patient is now able to regulate the release of AVP but only in the presence of the expanded total body water and hyponatremia. At this point the subject may respond in a normal fashion to a test load of water. This phenomenon might be anticipated from our earlier discussion of the continuous sensitive interrelationship between osmolar and nonosmolar stimuli controlling the release of AVP. There is a "resetting" of the "osmostat" created by the nonosmotic impulses impinging on the final common pathway or the magnocellular neurons of the neurohypophyseal system. For example, a cirrhotic patient with hyponatremia with a substantially expanded total body water may have a distinct water diuresis when a sustained water load (1,000 to 1,500 ml) causes a further decrease in the osmolality of the patient's body fluids. During this diuresis, if hypertonic saline is infused, an antidiuresis with the production of a hypertonic urine will occur as the serum becomes less hyposmotic. This indicates that the normal osmotic stimuli now produce an appropriate homeostatic response of the neurohypophyseal system. It is evident, therefore, that a normal water diuresis in this new steady state does not rule out the possibility that the initial water retention was produced by sustained nonosmotic release of AVP. An edematous patient in whom this water-excess syndrome *(hypervolemic hypernatremia)* develops (Table 13), in association with severe congestive heart failure, the nephrotic syndrome, cirrhosis of the liver, or some other disorder that functionally reduces GFR, enhances the

release of aldosterone and inhibits the humoral natriuretic "third factor,"[117,118] may have urine that is free of sodium rather than have the "salt-wasting" phase described above.

A most unusual example of the conversion of a salt-wasting to a salt-retaining state was described by Heinermann and Laragh.[260] Two cases of neoplastic disease (oat cell carcinoma of the lung and adenocarcinoma of the stomach) accompanied by the syndrome of hyponatremia, including excessive renal sodium loss, were studied. Both patients had normal renal and adrenal function, which in one was unquestionably due to a sustained inappropriate secretion of AVP. While under observation occlusion of the vena cava developed in both patients, and the hyponatremic salt-wasting state was converted to one of progressive sodium retention and edema formation. In the one with an occlusion of the superior vena cava, the salt retention occurred without an increase in aldosterone secretion; in the other with occlusion of the inferior vena cava, the edema formation occurred in association with hypersecretion of aldosterone. Thus, the disorders of these two patients closely resembled the hyposmolar syndrome seen in other edematous states.

Most recently an increasing number of reports of diuretic-induced (especially thiazide) and chlorpropamide-induced hyponatremic water intoxication syndromes have appeared.[133,229,261-264] Fichman and colleagues[135] studied 25 cases of severe hyponatremia resulting primarily from the use of thiazide diuretics in nonedematous patients without signs of dehydration and with normal creatinine clearance. These cases could be distinguished from other hyponatremic syndromes (Tables 14, 15, 18 and Figure 41) by the presence of hypokalemia and alkalosis, the return of serum sodium to normal and unimpaired excretion of a water load within 3 to 10 days after withdrawing the diuretic, and the recurrence of hyponatremia within 2 to 12 days of readministering the drug (Figure 45). Bioassays of the plasma while the patients were severely hyponatremic showed elevated AVP levels in all ten patients. In Figure 46, the concentration of AVP in these patients is compared with that found in the plasma of 23 cases of the typical syndrome of inappropriate secretion of AVP of varied cause and that of ten patients with secondary adrenal insufficiency associated with pituitary disease. Simultaneous isotope dilution studies in ten of the patients with diuretic-induced hyponatremia showed a substantial decrease in exchangeable potassium, but only a borderline decrease in exchangeable sodium. Increasing potassium intake improved the hyponatremia or prevented its development. The authors concluded that these patients represented a small proportion of those ingesting diuretics in whom potassium depletion rapidly developed after relatively small doses of the drug. The minimal and usual diuretic-induced sodium loss, when associated with hypokalemia and potassium depletion, possibly caused an exaggerated and sustained stimulation of the baroreceptor mechanism controlling the release of AVP. The persistent high level of AVP in the circulation was then primarily responsible for the impaired water excretion and its consequences. Other explanations for the abnormal AVP release include a direct effect of potassium deficiency on the neurohypophyseal system or an indirect effect by PGE enhancement on AVP release.[34-36,186] Finally, an impairment of the ability to excrete free water

TABLE 18.—*Differential Diagnosis of Hyponatremia With Normal Hydration**

	Inappropriate ADH Secretion	*Hypopituitarism*	*Hypothyroidism*	*Diuretic-Induced*	*Chlorpropamide-Induced*	*Polydipsic Vomiting*
Creatinine clearance	Normal	Normal or slightly low	Normal or slightly low	Normal or slightly low	Normal	Normal
Serum K^+ potassium	Normal	Normal	Normal	...	Normal	...
Serum bicarbonate	Normal	Normal	Normal	...	Normal	...
Urine Na^+ sodium	...	...	...	Early,later	...	...
Urine osmolality	...	...	...	Early,later	...	...
Metapyrone response	Normal	...	Normal	Normal	Normal	Normal
Water load response	...	...	Delayed	Normal	Delayed	Normal
Treatment	Water restriction	Hydrocortisone	Thyroid	Discontinue diuretics or potassium intake	Discontinue chlorpropamide	Sodium chloride, water restriction

*From Fichman MP, Vorherr H, Kleeman CR, et al: Ann Intern Med 75:853-863, 1971.

may occur in the absence of circulating AVP as thiazide diuretics prevent the reabsorption of sodium salts in the distal convoluted tubule and, possibly, in the cortical collecting duct.[264]

In the section on diabetes insipidus we discussed in detail the mechanism by which chlorpropamide can cause antidiuresis and thereby impair water excretion. Once this effect of the oral hypoglycemic agent was realized, it was not long before hyponatremia and water intoxication were reported, owing to its use in the treatment of diabetes mellitus.[229,262,263] Garcia and associates,[252] after observing two elderly diabetic patients (aged 71 and 76) with this syndrome, gave chlorpropamide to six additional persons with adult-onset diabetes and studied the response to an oral water load before and after drug administration. All the patients had a substantially impaired water diuresis with chlorpropamide. Twenty-three normal subjects, studied in a similar manner, also had a decrease in their maximal water diuresis, but the decrease was significantly less than that observed in the diabetic patients. It is possible that chlorpropamide is capable of greater inhibition of AVP-stimulated renal PGE synthesis in adult-onset diabetic patients than it is in nondiabetic subjects and, therefore, any residual AVP remaining in the circulation in a water-loaded or water-excess state can cause a greater degree of antidiuresis or impaired water excretion in diabetic persons.

The reason why relatively few patients using chlorpropamide develop hyponatremia and water intoxication is unclear. Theoretically, in all patients and normal subjects receiving chlorpropamide, water retention and hyponatremia should be minimal. The drug should initially cause an inappropriate antidiuresis, leading to a mild positive water balance and hyposmolality. This should inhibit the release of AVP on an osmotic basis, initiate a water diuresis and return water balance *almost* to normal. The data reported by Garcia and associates[252] and others[229,263] strongly suggest that in some patients with diabetes mellitus, particularly the elderly, a sustained nonosmotic stimulus to the release of AVP persists despite the substantial positive water balance. The frequent degenerative changes in the cardiovascular system

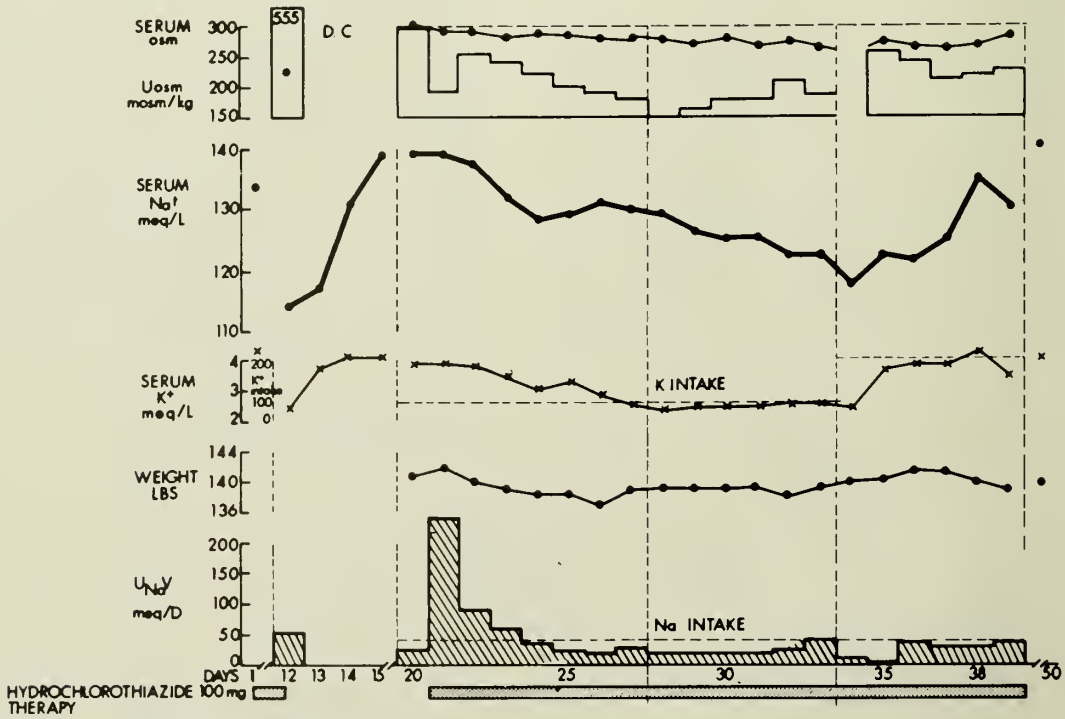


Figure 45.—Improvement in diuretic-induced hyponatremia with potassium (K^+) loading. The crosshatched bars at the bottom of the figure represent the 24-hour urine sodium Na^+); the horizontal dashed line at the bottom, the Na^+ intake; and the horizontal dashed line in the center, the K^+ intake, which was changed from 80 to 210 mEq per day. At the top of the diagram, the open bars indicate the urinary osmolality; the circles, the serum osmolality, and the dashed line, the normal serum osmolality of 290 mOsm per kg of body weight. (Reproduced with permission from Fichman MP, Vorherr H, Kleeman CR, et al: Ann Intern Med 75:853-863, 1971.)

of diabetic patients may cause abnormal functioning of those baroreceptor mechanisms modulating the secretion of AVP (see Table 3 in Part I). Alternatively, in these patients AVP secretion could be the result of a direct action of chlorpropamide on the CNS.

Studies of two unusual groups of patients with water intoxication have been reported recently. One was a group of patients with beer potomania, all of whom ingested large quantities (many gallons per day) of beer.[265] Coma and other neurologic signs were present, and serum sodium levels ranged between 98 and 120 mEq per liter. The authors concluded that low sodium intake (the "beer diet"), absorption of large quantities of water and, possibly, some form of inappropriate secretion of AVP accounted for the syndrome. It is of interest that several of the patients were also ingesting various types of diuretic drugs for hypertension, possible heart failure or steroid-induced edema. The other group consisted of psychotic patients who appeared to actually "drink themselves" into water intoxication without a known cause for impaired water excretion.[266] It is clear that despite their striking polyuria even those patients with profound polydipsia associated with severe emotional illness in whom a hyposmolar syndrome developed must have had some relative defect in water excretion. If we assume that at normal rates of solute excretion the maximal free water clearance is at least 10 percent of the simultaneous GFR, then a patient with a GFR of 120 ml per minute could excrete 12 ml per minute of free water—that is, clearance of free water would equal 17,280 ml per 24 hours. It is almost inconceivable, therefore, that patients could "drink themselves" into a severe hyposmolar state if there is inhibition of AVP secretion or if the drugs they are therapeutically ingesting can cause a sustained release of AVP that cannot be homeostatically inhibited by hyposmolality of their body fluids. Raskind and co-workers[267,268] have recently reported that plasma AVP levels were elevated in randomly selected untreated psychotic patients (Table 19). However, the mean plasma osmolality of these patients was normal. For dilution of body fluids to occur there must be impairment of water excretion as well as enhanced water intake (in excess of obligatory and insensible losses). The relative infrequency of severe hyponatremia in psychotic patients may be a reflection of normal or reduced water intake. Conversely, enhanced water intake by itself (up to 20 liters per day) is rarely associated with severe hyponatremia.

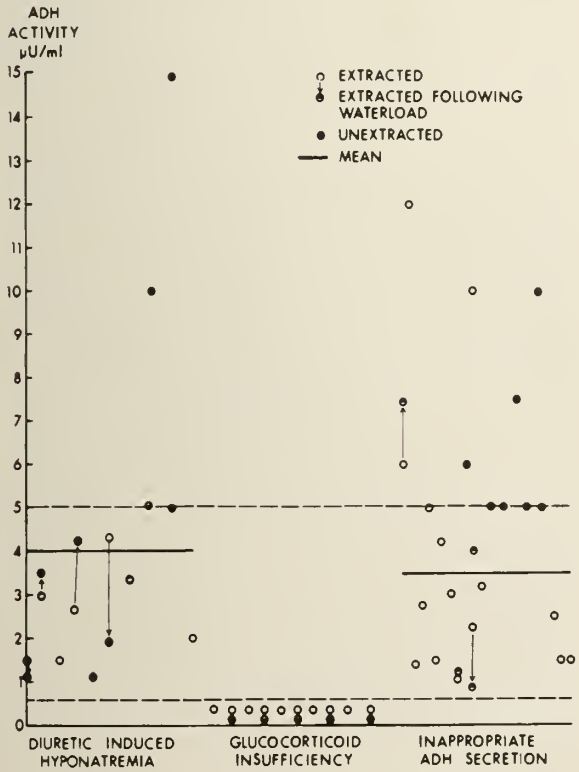


Figure 46.—Results of bioassay for vasopressin activity in plasma samples of 43 patients with hyponatremia caused by diuretics **(left)**, glucocorticoid insufficiency **(middle)** or inappropriate ADH (antidiuretic hormone) secretion **(right)**. The solid circles represent ADH activity in unextracted samples, the open circles ADH activity in extracted samples before water load, and the semisolid circles ADH activity in extracted samples after a water load of 20 ml per kg of body weight, with arrows connecting specimens from the same patient before and after the water load. The dashed lines represent the lower limit of sensitivity of the assay for unextracted (5 μU per ml) and extracted (0.5 μU per ml) samples; the solid horizontal lines represent the mean values for each group. (Reproduced with permission from Fichman MP, Vorherr H, Kleeman CR, et al: Ann Intern Med 75:853-863, 1971.)

In recent years the number of drugs that have been implicated in the production of a state of hyposmolar water retention has increased strikingly. Table 20 lists these drugs and the probable mechanisms by which they impair water excretion. It is certain that the number will increase.

The last major category of hyponatremic states is designated *hypervolemic hyponatremia*. In this situation there is a substantial expansion of total body sodium with even further expansion of total body water. In spite of these elevations, there is a substantial diminution in effective plasma vol-

ume. This is usually the result of decreased cardiac output and high venous pressure as in heart failure and sequestration of ECF volume in the form of ascitic fluid as in cirrhosis. In all these states there is diminished effective renal blood flow which produces substantial sodium retention by both the renin-angiotensin system and renal autoregulatory mechanisms.

The signs and symptoms associated with these conditions will depend, of course, on the underlying disorder that causes the impaired water excretion. The specific manifestations of the hyposmolar state will depend on the rapidity with which it develops and the severity of the hyponatremia. The old and the very young are most susceptible to its adverse effects. If we are dealing with a state of pure water retention that has developed slowly over weeks to months, it is surprising how asymptomatic the patient may be despite concentrations of sodium well below 120 mEq per liter (osmolality usually less than 240 mOsm per liter). However, when hyposmolality of this degree develops rapidly over days to a week or so, the manifestations of disturbed brain function, owing to overhydration of the CNS, may be profound. In addition to progressive depression of the sensorium (confusion, lethargy, headache, stupor and coma), any type of focal neurologic brain syndrome may occur including, finally, focal or generalized convulsions. Recently, Arieff and associates,[269] in a prospective study of a large number of patients with acute (days) and chronic (weeks) hyposmolality, stressed the danger to life of the acute production of water intoxication with concentrations of sodium below 120 mEq per liter. In addition to an in-depth review of this subject, they presented new experimental data on acute and chronic water intoxication in rabbits. The more acutely the same degree of severe hyponatremia (100 mEq per liter) was produced, the higher the mortality. Similar degrees of hyposmolality were very well tolerated by the animals when produced over several days. By analysis of brain tissue for its water, electrolyte and osmole content, Arieff and colleagues showed that when severe hyponatremia developed slowly there was significantly less edema or overhydration of the brain than when it developed rapidly, even when serum sodium levels were the same in the rabbits. The difference was due to the fact that the brain compensated by losing osmoles (sodium, chloride and potassium) when water intoxication was produced more slowly; therefore, less water moved into the brains of these animals on an osmotic differential basis. They "sacrificed" brain solute to prevent brain swelling and death.

TABLE 19.—*Elevated Plasma AVP in Psychosis**

Variable = SEM	*AVP, Units/ml Standing*	*AVP, Units/ml Supine*	*Plasma osmolality, mOsm/kg*	*Number*
Psychotic ..	3.47±0.45†	2.49±0.56	288±2.04	8
Anxious ...	1.6 ±0.23	1.65±0.22	288±1.36	8
Normal control ..	1.71±0.29	1.39±0.31	290±1.60	8

AVP = arginine vasopressin; SEM = standard error of the mean.

*Modified with permission from Raskind M, Weitzman R, Orenstein H, et al: Antidiuretic hormone in psychosis, a pilot study. Biol Psychiatry 13:385-390, 1978.
†P = 0.05

TABLE 20.—*Drugs Associated With Hyponatremia*

Principal Mechanisms

Augmented thirst
- Mellaril (thioridazine)

Augmented renal action of AVP
- Chlorpropamide
- Tolbutamide
- Acetaminophen*
- Phenformin
- Indomethacin*

Impaired renal water excretion independent of AVP
- Chlorpropamide
- Clofibrate
- Carbamazepine
- Vincristine
- Vinblastine
- Cyclophosphamide
- Opiates
- Histamine

Nonosmolar stimulation of AVP release (baroreceptor-mediated)
- Thiazides (?)
- Isoproterenol
- Nicotine
- Barbiturates (?)

AVP = arginine vasopressin

*Enhances AVP action but is not associated with hyponatremia.

Therapy of the Hyponatremic State

Once it is decided into which category a hyponatremic patient belongs, a rational therapeutic approach can be planned. The patient's history preceding the detection of the hyposmolality, symptoms and physical signs, as well as certain critical chemical analyses of blood and urine, when combined with the patient's change in weight and approximated water balance, can permit categorizing the patient's condition (Tables 14, 18 and Figure 41).

Salt- and volume-depleted patients (hypovolemic hyponatremia), when supplied with adequate

amounts of isotonic or, occasionally, hypertonic saline solution, will make whatever final renal adjustments are necessary to maintain ICF and ECF volumes and tonicity at normal levels. This, of course, implies a neurohypophyseal system *appropriately* responsive to the removal of nonosmotic stimuli, and basically normal kidneys that can respond to the neurohumoral adjustments which follow the replacement of salt and water. This is the usual situation associated with an extrarenal cause for the salt and water depletion. Unfortunately, when a functional (excess diuretics, adrenal insufficiency) or organic (salt-losing nephropathy) disorder of the kidney is responsible, the renal adjustment may not be completely appropriate. Therefore, the functional causes must be corrected, and the impact of the organic lesion on the homeostatic excretion of salt and water must be taken into consideration during replacement therapy.

In cases belonging in the second category (hyponatremia with minimal hypervolemia) (Table 14), a primary excess of total body water with normal or minimally decreased total body sodium, once diagnosed, must be corrected by the creation of a negative water balance and, at times, the administration of hypertonic saline to restore the osmolality of body fluids to normal. At the same time that the hyposmolality is being treated, every effort to remove or correct the underlying cause of the impaired water excretion should be made (Tables 15 and 16). Given a patient with a "water excess" syndrome the choice of therapy will depend on the severity of the hyposmolality, the rapidity of its development and the magnitude of the "water intoxication." Basically, a negative water balance must be created, and the first therapeutic maneuver should be the restriction of water intake to the lowest possible level. The drier the diet, the better. In most cases, this will be adequate until the underlying cause can be corrected. Serum sodium and osmolality should be returned to normal levels. Urine volume will decrease further under this therapy, but this will be of no consequence as long as the patient remains in negative water balance through renal and extrarenal routes. The only exception to this approach may be for patients with so-called asymptomatic hyponatremia who have inappropriate or ectopic secretion of AVP and in whom a hyposmolar state has slowly developed over many weeks or longer. In these patients serum sodium levels are between 120 and 130 mEq per liter and CNS and other tissues have adjusted to their hypotonic environment.[269] These patients may not look or feel better when the osmolality of the body fluids is normal. Furthermore, because the underlying cause for the SIADH often cannot be readily removed, hyponatremia will rapidly return when water intake is made more liberal.

In striking contrast to these patients are those who are truly water intoxicated. The impaired water excretion relative to intake, due to the causes listed in Table 16, develops over hours to days and often reaches a point where serum sodium is below 120 mEq per liter. All the symptoms and signs described earlier may present and seriously threaten the life and recovery of these patients. In this situation the foremost objective is to correct the severe cellular overhydration, particularly of the cells of the CNS. This can be accomplished by rapidly (hours) increasing the *effective* osmolality of the ECF while continuing the water-restriction regimen. Hypertonic saline (5 percent) or hypertonic mannitol (10 percent to 20 percent) makes up the effective osmotic solutes. One can estimate the approximate expansion of total body water in these patients by calculating the volume of total body water required to dilute the serum sodium concentration to its observed value. Total body water (BW) is estimated as 60 percent of total weight in women and 65 percent of total weight in men of average body composition. One then multiplies a patient's normal total body weight times a normal total serum sodium concentration and then divides it by the observed serum sodium concentration to get the total body water in the hypotonic state. As mentioned above, such calculations frequently overestimate the true amount of weight gain from the premorbid state.

$$BW = 70\ kg \times 0.60 = 42\ liters$$
$$X \times 120\ mEq/liter = 42 \times 140\ mEq/liter$$
$$X = 49\ liters$$

Therefore, total BW in the abnormal state (X) is approximately 49 liters, or 7 liters greater than normal. The amount of sodium in milliequivalents required for correction of the hyponatremia can then be calculated by multiplying the difference between the observed sodium concentration and a desired concentration times the total body water. While it is clear that the salt is actually distributed in ECF, the rise in osmolality that it creates at any given point continuously draws water out of the cells along the newly established osmotic gradient until at any given new steady

state the rise in osmolality or sodium concentration is as though the salt were distributed in a volume equivalent to total body water. The serum sodium should be elevated approximately 10 percent to 15 percent over the first eight to ten hours of therapy.

The correction of cellular overhydration will almost always be associated with pronounced improvement in the CNS symptoms and signs during the first 24 hours if they are due to the water intoxication. Occasionally, in older patients (over 65 years), the rate of recovery may be delayed an additional 24 to 48 hours. It is also in this

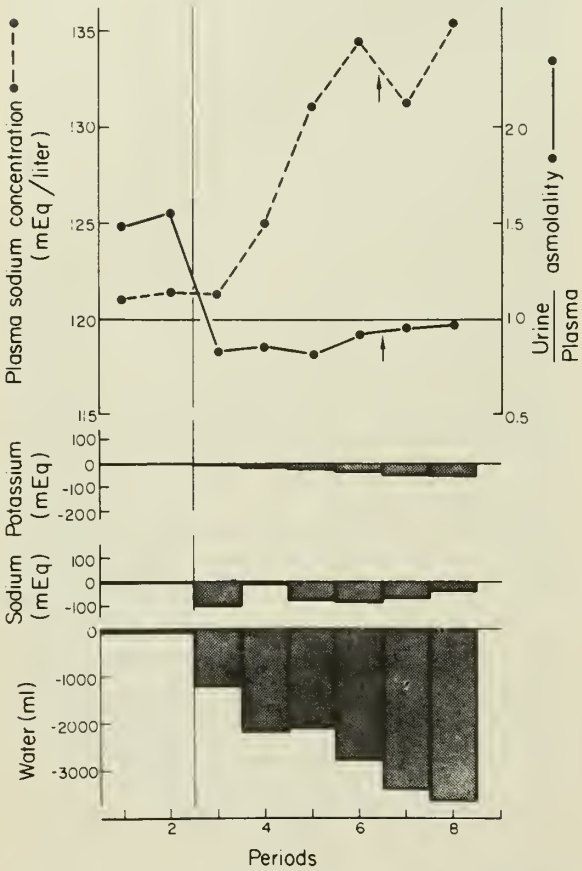


Figure 47.—Use of furosemide and hypertonic saline in the rapid correction of hyponatremia in a patient with the syndrome of inappropriate secretion of antidiuretic hormone. The control periods in this figure are separated from the periods following the administration of furosemide by vertical lines. The arrows indicate the point at which the last dose of furosemide was given. Each period equals one hour. Administration of furosemide was associated with hypotonic urine and increased plasma sodium concentration in the absence of either a positive sodium or positive potassium balance. The cumulative potassium, sodium and water balances are shown in the bottom three panels of the figure. (Reproduced with permission from Hantman D, et al: Ann Intern Med 78:871, 1973.)

age group that the large salt load and rapid expansion of the extracellular volume, over and above that created by the original water retention may precipitate acute congestive heart failure. This reason and the desire to greatly increase the rate of salt and water excretion, led Hantman and associates[270] to suggest the combined use of hypertonic saline and a potent diuretic such as furosemide (Lasix) at an initial dose of approximately 1 mg per kg of body weight given intravenously. This approach is illustrated in Figure 47. This "loop" diuretic by inhibiting the active reabsorption of sodium chloride in the thick ascending limb (1) prevents excessive ECF volume expansion during and immediately following the saline infusion, (2) substantially impairs the function of the medullary countercurrent multiplier system so that concentrated urine cannot be produced despite the excess circulating AVP and (3) causes the excretion of large amounts of water and sodium in a concentration below that of the plasma and, thus, greatly below that of the administered hypertonic saline. The net effect of this therapy is a large negative water balance produced in a matter of hours associated with a rapid (hours) return of plasma osmolality to normal (Figure 47). An adverse trade-off of this approach is the simultaneous diuretic-induced renal loss of potassium and magnesium ions. This may cause the rapid development of hypokalemia and hypomagnesemia. The former may have immediate deleterious effects which should be anticipated and prevented by simultaneous administration of 150 to 200 mEq per liter of potassium during the first 24 hours of therapy. The excretion of this amount of potassium (in 24 hours) would not be unusual during the diuretic-induced natriuresis. Magnesium excretion may reach 15 to 20 mEq or 180 to 240 mg at the same time. Its rapid development depends on the presence of any degree of hypomagnesium and potassium when serum osmolality and sodium are determined, and the rate of excretion of these ions (magnesium and potassium) during the diuresis.

Hypertonic mannitol has been suggested as an alternative to hypertonic sodium chloride for the treatment of hyposmolar states, but its use offers no particular advantages and has several possible disadvantages compared with hypertonic saline.[247,271]

Three drugs that specifically inhibit the secretion or renal effect of AVP have been used in the treatment of SIADH. These are diphenylhydantoin

(Dilantin) which when administered intravenously can block the release of AVP from the neurohypophysis,[272] dichlormethyltetracycline (Declomycin, demeclocycline)[273] and lithium.[274] Both of these latter compounds act by directly blocking the renal tubular effect of AVP. They appear to have a role in patients in whom the syndrome is not self-limited and in whom the underlying cause cannot be removed. In such settings (for example, AVP-secreting bronchogenic carcinoma), a drug that could be taken by mouth and for a prolonged period would be most desirable. While both have untoward and toxic effects, the antibiotic dichlormethyltetracycline in dosages of 1 to 2 grams per day would be least objectionable. With greater experience in the use of this drug, we will be better able to define its practical limitations.

Glucocorticoids and Water Excretion

The inability to excrete a water load in a normal manner is characteristic of primary and secondary adrenal insufficiency. This defect is due to a deficiency of cortisol, and it continues to be seen in the presence of a normal extracellular volume and adequate mineralocorticoids.[251] These persons are unable to form a maximally dilute urine or to attain a maximal rate of water diuresis after either an acute or chronic water load and, therefore, are particularly prone to the development of water intoxication. The continued production of a hypertonic urine relatively low in volume during a sustained positive water load suggests the possible presence of continued circulating AVP. However, to date the evidence is still inconclusive in both humans and animals as to the exact role of AVP in the impaired water excretion of primary and secondary adrenal insufficiency. It is clear that if a patient with primary or secondary adrenal insufficiency has hypovolemia, hypotension or reduced cardiac output (see Table 3 in Part I), it could cause a sustained release of AVP which would contribute to an impaired water excretion resulting from a nonhormonal mechanism. Share and Travis[275] showed in trained unanesthetized dogs with excised adrenal glands that if blood and extracellular volume were maintained at normal levels by a liberal intake of sodium chloride, basal plasma AVP concentration did not increase. However, the concentration of AVP in the plasma rose progressively if the sodium chloride was withdrawn. Giving the animal a large dose of hydrocortisone at this point only slightly reduced the elevated AVP levels, whereas an infusion of saline without the steroid administration returned the plasma AVP almost to normal. Additional experimental evidence against a *primary* role of AVP in the impaired water diuresis of adrenal-insufficient humans or animals was given by Green and co-workers[276] who showed that the diuresis is equally impaired in adrenalectomized rats with hereditary DI (Brattleboro strain). Arginine vasopressin *cannot* participate in the defect in water excretion in these adrenal-insufficient animals. Using a sensitive bioassay, our findings indicated a normal disappearance of AVP from the circulation of untreated patients with adrenal insufficiency despite impaired diuresis.[133,251] In these patients there was no delay in activation of, or increased sensitivity to, exogenously administered AVP. Although their peak water diuresis was subnormal, the rate at which this level was attained was comparable to that observed in normal persons.[251] Ahmed and associates[277] and, recently, others[278] have implicated sustained circulating AVP in the impaired water diuresis of primary or secondary adrenal insufficiency. However, it is reasonable to conclude that the sustained circulating AVP is not essential for this defect in water excretion.

If the latter is correct, why do these patients have this physiologic abnormality? Certainly, any reduction in GFR or renal blood flow would impair the attainment of a maximal water diuresis. Both GFR and renal blood flow have been found to be moderately reduced in patients with adrenal insufficiency, and hemodynamic abnormalities are corrected by adequate therapy with glucocorticoids. However, rapid administration of hydrocortisone during impaired water diuresis can substantially improve the rate of urinary flow and the production of a maximally dilute urine with little or no acute alteration in renal hemodynamics.[279] Nonhormonal techniques that considerably improve renal blood flow and GFR, such as aminophylline administration, do not appreciably enhance the water diuresis.[279] These observations suggest that the glucocorticoids improve water diuresis through some intrarenal mechanism that ultimately causes a decrease in the back diffusion of water in the diluting segments of the nephrons. It is also possible that these steroids allow these segments to become maximally impermeable to water in the absence of AVP. This could be considered a "permissive" role of the glucocorticoids.

The pure water-excess syndrome secondary to the sustained release of AVP can be almost mi-

micked by primary and secondary adrenal insufficiency (glucocorticoid deficiency). In the latter circumstances the hyponatremia and relative or absolute excess of total body water can be quickly corrected by the oral or intravenous administration of glucocorticoids; in contrast, the syndrome of inappropriate secretion of AVP not associated with glucocorticoid deficiency will not be corrected by steroid administration.[133,280,281]

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Symposium on Adolescent Gynecology and Endocrinology

Part III: Venereal Diseases in Adolescents and Contraception in Teenagers

Venereal Diseases in Adolescents

PHYLLIS A. OILL, MD*

VENEREAL DISEASE is epidemic in the United States, with gonorrhea ranking first and syphilis third among the nationally notifiable diseases.[143] Adolescents aged 15 to 19 and adults from 20 to 24 bear a disproportionate share of the increase in reported gonorrhea infections, and of the absolute number of cases. More than two thirds of all reported cases of gonorrhea occur among persons younger than 25 years, with one of every four reported cases occurring among adolescents (persons 10 to 19 years of age).[143,144] In 1975, there were 266,613 cases of gonorrhea and 3,719 cases of infectious syphilis reported in the 15 to 19 age group. Reported cases of venereal disease represent only a small part of the problem because private physicians treat about 80 percent of the diagnosed gonorrhea and syphilis cases, and report only about one in nine cases of gonorrhea and one in eight cases of syphilis.[145] It is conservatively estimated that about one adolescent actually becomes infected with either syphilis or gonorrhea each minute, or that 1,700 infections occur each day, for well over half a million each year.[146]

The adolescent period is one of rapid and often chaotic change, with adolescents dealing with the important psychological task of self-identity or self-concept which is involved in defining the sexual being.[147] It is sexual activity that places one at risk for venereal disease and adolescents by definition are increasingly sexually active, and tend to base their maturity level upon sexual involvement.[148] The combination of the adolescent's sexual exploration, more permissive societal acceptance of sexual attitudes and behaviors, and the technologic advances in contraception are all implicated in the venereal disease epidemic.[149,150] Additionally, the fact that asymptomatic gonococcal disease occurs in a significant number of females and males[151-153] further complicates the problem. Table 7 lists the factors associated with the venereal disease epidemic in adolescents.

There are numerous diseases that are acquired or spread by sexual contact. The following is a

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TABLE 7.—*Factors Implicated in Adolescent Venereal Disease*

Sexual permissiveness
Self-definition
Contraceptive use
Attitudes and education
Asymptomatic disease
Male homosexuality

brief discussion of the most common of the sexually transmitted diseases affecting adolescents.

Gonorrhea

Gonorrhea is spread almost exclusively through sexual contact. A single contact with an infected female is estimated to carry with it a 22 percent risk of infection for her male consort.[154] The disease is caused by *Neisseria gonorrhoeae,* a Gram-negative coccus that can penetrate and readily infect mucous membranes. The disease has diverse clinical syndromes, and only an overview will be given since a number of extensive reviews have been published.[155-158]

Asymptomatic disease occurs in both males and females, with females accounting for most of the asymptomatic infections.[151,159] The incubation period for gonorrheal urethritis in the male is usually two to eight days with the sudden onset of dysuria, and urinary urgency and frequency. There is an associated mucoid discharge that rapidly becomes purulent and profuse. The patient is afebrile, and without treatment the symptomatic urethritis may spontaneously resolve over a period of weeks. Direct spread of the infection may result in prostatitis, epididymitis and seminal vesiculitis.[160] These infections are often associated with fever.

In females, disease may begin with dysuria, and urinary urgency and frequency after an incubation period of two to eight days. However, symptomatic urethritis is frequently of short duration and often mild or asymptomatic. Endocervicitis gives rise to a mucopurulent discharge that varies from scant to profuse. A history of increased vaginal discharge and dysuria five to ten days after intercourse or occurring just after menstruation is suggestive of gonorrhea. Coincidental vaginal discharge from monilia, trichomonas, or other vaginal or cervical infections is common.[161] Contiguous spread can cause salpingitis which is usually bilateral and many lead to pyosalpinx and formation of tubo-ovarian abscess. Involvement of Bartholin and Skene glands is common and abscess formation may occur.[162]

Proctitis is usually asymptomatic, but may be manifested by anal discharge, burning rectal pain, blood and pus in the stool, and pain on defecation.[163] In females, proctitis may occur secondary to contiguous spread from infected vaginal secretions to the anal area, or by direct implantation of the organism during anal intercourse.[164] Pharyngitis is also usually asymptomatic, but gonorrhea probably can cause symptomatic pharyngitis, tonsillitis and gingivitis.[165] In females, pharyngitis is found in those who practice fellatio. In men, pharyngitis and proctitis are encountered in those who have homosexual contacts.

Occasionally, invasion of the blood occurs and *N gonorrhoeae* may disseminate and produce infection at a distant focus. Joints are the most frequent extragenital sites of localization, but tenosynovitis, skin lesions, hepatitis, endocarditis, meningitis and infection at other foci may also occur.[166,167] Dissemination probably occurs more frequently in females because they are more often asymptomatic and constitute the largest reservoir. It is clinically often associated with pregnancy or menstruation.

In males, Gram stain of urethral exudate shows Gram-negative intracellular diplococci (95 percent sensitive and specific). A culture must be obtained when the patient is asymptomatic or smear is nondiagnostic. Culture from pharynx and anorectum is also necessary in homosexual males. In females, cultures need to be obtained from the endocervix and anorectum. Gram stain only reaches 50 percent sensitivity in gonorrheal cervicitis. Culture from the pharynx is also necessary in patients who practice fellatio. In disseminated gonococcal infection, cultures should be obtained from the blood, skin lesions and joint effusion, if present. In addition, culture from the urethra or cervix, pharynx and anorectum is necessary because disseminated disease has been reported as originating from any one of the above sites. The specimens should be inoculated directly onto culture medium. Culture medium of choice is Thayer-Martin medium or a suitable transport medium (such as Transgrow) for sites where other organisms usually reside. Chocolate agar medium is used for those sites that are usually sterile (such as synovial fluid and cerebral spinal fluid).

Recommendations for treatment for both uncomplicated and complicated gonorrhea have been issued by the Center for Disease Control.[168] Uncomplicated gonorrhea in both males and females is preferably treated with aqueous procaine peni-

cillin G, 4.8 million units given by two intramuscular injections at a single visit, along with 1 gram of probenecid given orally. Alternatives to parenteral administration of penicillin G are oral administration of ampicillin, 3.5 grams, or amoxicillin, 3.0 grams, with 1 gram of probenecid. Patients allergic to penicillin may be treated with tetracycline hydrochloride, 0.5 gram given by mouth four times a day for five days (total dosage 10.0 grams). A single injection of spectinomycin hydrochloride, 2 grams intramuscularly, should be administered to patients with allergy to both penicillin and tetracycline and in cases of treatment failures or infection with penicillinase-producing organisms.[168,169] Disseminated gonococcal infections may require admission of the patient to hospital and administration of aqueous penicillin G, 10 million units per day intravenously, until there is clinical defervescence of symptoms, followed by orally given ampicillin, 0.5 grams four times a day to complete a seven day course. Oral therapy with ampicillin, amoxicillin or tetracycline is also efficacious.[168] Males and females with known recent exposure to gonorrhea should receive the same treatment as persons known to have gonorrhea.

Follow-up urethral and other appropriate cultures should be carried out in men, and cervical, rectal and, if indicated, pharyngeal cultures should be done in women 7 to 14 days after completion of therapy. This is now recommended routinely.

Syphilis

Syphilis accounts for less than 1 percent of the venereal disease encountered in adolescents[171,172] and, untreated, has significant consequences later in adulthood. *Treponema pallidum,* a spirochete, is transmitted through direct contact with an infectious lesion, and invades intact mucous membranes and abraded skin. Reviews of this disease have been published.[174-176]

Primary syphilis develops after an incubation period that ranges from 10 to 90 days. The classical chancre appears initially as a papule, which then evolves into an indurated, painless, ulcerative lesion with raised, firm borders.[173] It is usually accompanied by bilateral, discrete, painless inguinal adenopathy. Careful examination is necessary to identify lesions in the vulvar area, cervix, perirectal skin and rectal mucosa. Extragenital sites, such as the fingers, lips, pharynx and tongue, can also be involved. The primary lesion heals in one to six weeks without treatment.

Secondary syphilis occurs approximately two to ten weeks after the appearance of the primary lesion, and lasts from one to six weeks. This stage is heralded by a rash which is usually bilaterally symmetrical, can involve the palms and soles, may be macular, papular, follicular or papulosquamous, and, rarely, pustular or nodular.[176] It is usually dry and nonpruritic. Condylomata lata, another skin manifestation, are flat, moist papules which occur primarily in the intertriginous areas. Constitutional symptoms, which may precede or accompany the lesions, include headache, malaise, anorexia, fever, sore throat and generalized lymphadenopathy.[174]

In the hands of an experienced physician, a dark-field microscopic examination of material scraped from lesions is the single most accurate test in diagnosing primary syphilis. Additionally, serologic tests can confirm the diagnosis. A VDRL test becomes positive in 10 to 90 days following the initial lesion. In approximately 50 percent of infected persons a VDRL test is positive within the first three weeks, while in 90 percent it is positive at six weeks. A positive VDRL test is present in essentially all cases of secondary syphilis. The fluorescent treponemal antibody absorbed test (FTA-ABS) can be used to confirm the diagnosis and eliminate biologic false-positive VDRL tests.[177] When dealing with adolescents, a population at risk for drug abuse as well as venereal disease, the possibility of a biological false-positive VDRL secondary to heroin abuse must be considered.[178]

The drug of choice in the treatment of primary and secondary syphilis is benzathine penicillin, 2.4 million units given intramuscularly, administered in two sites at one visit. In a penicillin-allergic patient, tetracycline or erythromycin, 0.5 gram given orally four times a day for 15 days (total 30 grams) can be used as an alternative.[179] It should be noted that the procaine penicillin treatment of gonorrhea will treat *incubating* syphilis, but not primary disease.[180]

At the time of therapy it is prudent to advise the patient of the possibility of Jarisch-Herxheimer reaction, which occurs in over 50 percent of patients with primary and secondary syphilis.[181] It characteristically occurs within 12 hours of treatment and resembles an influenza-like syndrome of fever, lethargy, myalgia, headache and recrudescence of the rash. It is symptomatically improved by antipyretics. It is relatively insignificant among patients with early syphilis, and

alerting the patient about the reaction and home management prevent unnecessary patient alarm.[182]

Nonspecific Urethritis

Nonspecific urethritis (NSU), also known as postgonococcal urethritis or nongonococcal urethritis, is an inflammation of the urethra caused by organisms other than the gonococcus. It is exceedingly common in males: an estimated 2.5 million cases in 1976.[143] NSU may be caused by a variety of organisms, but *Chlamydia trachomatis* accounts for most of the diagnosed NSU.[183-185]

Generally, symptoms may be consistent with gonorrheal urethritis: dysuria, urethral discharge or urinary frequency. The discharge is usually scant and watery, although it may be purulent.[185]

The key to diagnosis is by laboratory means. Gram stain of the urethral discharge (expressed or obtained by swab) is imperative to rule out the presence of *Neisseria gonorrhoeae*. Exudates that contain polymorphonuclear leukocytes, but no Gram-negative diplococci, make the diagnosis.[186] Culture for *N gonorrhoeae* should be done routinely.

Treatment is with tetracycline, 0.5 grams given orally four times a day for seven days.[184] As part of the management of NSU, every attempt should be made to treat the patient's sex partner.

Herpes Genitalis

Herpes genitalis, caused by Herpesvirus hominis type 2 (HVH-2) is sexually transmitted with an estimated 300,000 new cases in 1976.[143] Adolescents may account for 25 percent to 50 percent of all patients with genital herpetic infection.[187] The virus infects cells by contiguous spread and then is thought to establish a latent infection in the dorsal root ganglia of the spinal cord. It is an endogenous virus, therefore, that is responsible for recurrent disease.[188]

The clinical features vary from person to person with up to 50 percent of all genital HVH-2 infections being asymptomatic.[189] Primary genital herpes occurs in patients without HVH-2 antibodies and can be severe, particularly in the female. Symptoms appear three to four days following exposure and include fever, headache, malaise, anorexia and lymphadenopathy. Lesions involve the external and internal genitalia and start as small, painful vesicles on an erythematous base which become ulcerative and heal in three to six weeks depending on the severity of the disease. Inguinal or pelvic pain, dysuria, dyspareunia and urinary frequency may also be present.[190]

Recurrent HVH-2 infections are milder than primary disease. Factors said to precipitate recurrences include temperature elevation, emotional disturbances, premenstrual tension, local trauma and severe systemic disease.[189] Lesions tend to occur in the same sites as primary disease, but are often inconspicuous. They are usually vesiculo-ulcerative lesions in localized patches. The vesicles rupture in 24 to 48 hours forming ulcers which crust and heal in seven to ten days.

The diagnosis can be confirmed by isolation of the virus, electron-microscopy of vesicular fluid, exfoliative cytology (Papanicolaou smear), cytologic examination or a fourfold rise in serum antibody titer against HVH-2. The cytologic examination (the Tzanck test) is the most simple and readily available. It is carried out in the following manner: scrapings from the base of the ulcer are fixed on a slide with absolute or methyl alcohol for ten minutes, and then stained with Giemsa. The finding of multinucleated giant cells or typical eosinophilic intranuclear inclusions (Cowdry type A) is diagnostic.[190]

Prevention and treatment of genital herpes infection is difficult because of the lack of knowl-

TABLE 8.—*Minor Sexually Transmitted Diseases*

Disease	*Clinical Features*	*Diagnosis*	*Treatment*
Chancroid	Multiple, painful, autoinoculable ulcers; painful inguinal adenopathy, unilateral buboes	History of exposure; clinical signs and symptoms; smears; culture	Sulfonamides Tetracycline Streptomycin
Lymphogranuloma venereum	Transient genital lesion; inguinal adenopathy with genital groove; proctitis; rectal strictures, elephantitic changes	Clinical signs and symptoms; Frei test; complement fixation	Sulfonamides Tetracycline Dilitation Surgical operation
Granuloma inguinale	Insidious onset; mildly tender ulcers with granular base; pseudobuboes; chronic impairment of health	Donovan bodies in spreads or biopsies; complement fixation test; clinical signs and symptoms	Tetracycline Streptomycin Chloramphenicol

TABLE 9.—*Estimated Numbers of Teenage Pregnancy in the United States in 1976**

Total	1,010,000	
Premarital	780,000	(77% of total)
Not intended	554,000	(71% of premarital)
No contraception	438,000	(79% of not intended)

*Reproduced by permission from Zelnik and Kantner.[197]

edge concerning immunity to infection, and the pathogenesis of recurrent infection. Little benefit has been obtained by using various immunizing agents (such as autoinoculation, smallpox vaccination, vaccine from inactivated HVH-2).[191] The mainstay of treatment is symptomatic therapy; antiviral agents, ether and photodynamic inactivation have not been shown to be efficacious either acutely or for recurrent disease. Local and systemic analgesics help in relief of pain. Mild antiseptic compresses (benzalkonium 1:4,000; potassium permanganate 1:6,000) can be applied three to four times per day to reduce the risk of bacterial infection. Systemic antibiotics should be administered only if secondary bacterial infection occurs. Steroids, given locally or systemically, are contraindicated.

Minor Venereal Diseases

Chancroid, granuloma inguinale and lymphogranuloma venereum account for less than 1 percent of all reportable venereal diseases.[143,146] Table 8 gives a brief summary of these diseases. The reader is referred to more comprehensive publications for detailed discussion of these diseases.[192-195]

Venereal warts, caused by papillomavirus, infect the genital and anal areas and approximately 700,000 infections occurred in 1976.[143] The appearance of genital warts is too familiar to require detailed description. The lesions are multiple and polymorphic, and may coalesce into large masses. In the male, they occur most often in areas subjected to trauma during coitus and are somewhat commoner in uncircumcised than circumcised males.[196] Anal warts in males are associated with anal intercourse and, therefore, are found in homosexual males. In females, warts often appear first at the fourchette and on the adjacent labia.[196] They occur on other parts of the vulva and in 20 percent of patients spread to the perineum and anus. The vagina and cervix can also be involved. Patients with anal warts should have anoscopy to evaluate the extent of involvement.

The best known treatment of genital warts is cytotoxic therapy with podophyllin, 10 percent or 25 percent solution in spirit of tincture of benzoin.[196] It is applied to the lesion, allowed to dry and washed off in three to four hours. The treatment is carried out once or twice a week, and if there has been no significant improvement in about a month then alternative therapy should be considered (cautery, diathermy, cryosurgery).

Conclusion

In summary, adolescence is a time of overt exploration of sexual identity. This exploration often leads to multiple sexual contacts and exposure to sexually transmitted diseases. Education of adolescents about venereal disease risks and aggressive diagnosis by physicians are necessary to ameliorate the present venereal disease problem in adolescents.

Contraception in Teenagers

DANIEL R. MISHELL, JR., MD

In the United States teenage pregnancy consitutes a problem of epidemic proportion. The number of births for women of most age groups in the United States is steadily decreasing so that this country is approaching zero population growth. However, there is an exception to this trend in the teenage population. The number of teenage pregnancies has remained relatively constant over the last five years despite the increased use of contraceptives.

In 1976 there were slightly more than 1 million teenage pregnancies in the United States. Of these, nearly four fifths, or 780,000, occurred in women who were not married—and of that group, 71 percent of the pregnancies were not intended (Table 9).[197] It was estimated, therefore, that there were 554,000 premarital pregnancies in the United States that were not intended. Of these pregnant women, 438,000 (79 percent) were not using contraception at the time that conception occurred. The problem of unintended teenage pregnancies persists, despite the fact that more teenagers than ever are using contraception because more teenagers are engaging in sexual activity.

Zelnik and Kantner carried out surveys of

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sexual and contraceptive experience among unmarried 15- to 19-year-old women in the United States in both 1971 and 1976. They found that there was a 30.2 percent increase in the incidence of premarital intercourse among never married teenagers between 1971 and 1976 (Table 10).[198] The percentage increase occurred at all ages and was greater in whites than blacks. By the age of 19 years, 55.2 percent of never married women have engaged in sexual intercourse. When comparing the results of these surveys, these investigators concluded that in the United States girls are having intercourse at an earlier age and with more partners but probably at about the same frequency as in the past. Zelnik and Kantner also found that the percentage of women aged 15 to 19 who had premarital first pregnancies increased from 9.0 percent to 11.6 percent between 1971 and 1976 (Table 11).[199] This increase occurred primarily among white teenagers, from 6.4 percent to 9.3 percent, while the 25.5 percent incidence of black teenagers who had premarital conceptions remained constant over this five-year period. The percentage of all teenagers who had premarital intercourse and conceived also remained relatively constant. Therefore, the increased percentage of teenagers who became pregnant was due to more women having premarital intercourse.

About 26.9 percent of sexually experienced teenagers use contraception always and another 31 percent never use it, with the remaining 42.1 percent using contraceptives occasionally (Table 12).[197] The incidence of premarital pregnancies is inversely proportionate to the use of contraception. Those who never use contraception have about a six times greater chance of conceiving than those who use contraception always, and about a two and a half times greater chance of conceiving than those who use contraception occasionally. In 1976, as noted above, 71.2 percent of premarital pregnancies in teenagers in the United States were not intended. Couples were using contraception at the time of conception in only 21.1 percent of these pregnancies (Table 13).[197] When contraception was used, about a third of the pregnancies, 7.4 percent, occurred while the couples were using the more effective medical forms of contraception. These methods, which include oral contraceptives, intrauterine devices or diaphragms, require a visit to a physician or clinic. The remaining two thirds, 13.7 percent, of these conceptions occurred while using less effective nonmedical types of contraception, such as rhythm, withdrawal, condoms or foam. In 78.9 percent of nonintended premarital pregnancies, the couples were not using contraception at the time the conception occurred.

Consistent use of effective contraception by teenagers would have had a dramatic impact on the number of unintended premarital pregnancies that occurred in teenagers in the United States in 1976. Of the 780,000 premarital pregnancies, 554,000 were not intended and 438,000 occurred without use of contraception. If no contraception had been used by teenagers premaritally, an addi-

TABLE 10.—*Percentage of Never-Married Women Aged 15 to 19 Who Have Ever Had Intercourse, by Age and Race, 1976 and 1971**

	Study Year and Race								
	1976			*1971*			*Percent Increase 1971-1976*		
Age	*All*	*White*	*Black*	*All*	*White*	*Black*	*All*	*White*	*Black*
15-19	34.9	30.8	62.7	26.8	21.4	51.2	30.2	43.9	22.5
15	18.0	13.8	38.4	13.8	10.9	30.5	30.4	26.6	25.9
16	25.4	22.6	52.6	21.2	16.9	46.2	19.8	33.7	13.9
17	40.9	36.1	68.4	26.6	21.8	58.8	53.8	65.6	16.3
18	45.2	43.6	74.1	36.8	32.3	62.7	22.8	35.0	18.2
19	55.2	48.7	83.6	46.8	39.4	76.2	17.9	23.6	9.7

*Reproduced by permission from Zelnik and Kantner.[198]

TABLE 11.—*Percentage of Women Aged 15 to 19 Having Premarital First Pregnancy**

	1971			*1976*		
	White	*Black*	*All*	*White*	*Black*	*All*
Women who had premarital first pregnancy	6.4	25.5	9.0	9.3	25.5	11.6
Women who had premarital intercourse	24.3	47.1	29.8	25.2	39.5	28.3

*Reproduced by permission from Zelnik and Kantner.[199]

tional 680,000 premarital pregnancies would have occurred. However, if contraception had been used consistently by all unmarried teenagers, the number of premarital teenage pregnancies would have dropped from 780,000 to 467,000, a decrease of 40 percent.[197]

To reduce the number of unwanted teenage pregnancies with their attendant psychological, sociological and economic problems, all teenagers engaging in sexual intercourse should use effective contraception consistently. Comparing the surveys of 1971 and 1976, Zelnik and Kantner found that the percentage of sexually experienced teenagers aged 15 to 19 who had always used contraception increased almost twofold, 18.4 percent to 30.0 percent, between 1971 and 1976, but there was also an increase in the number who had never used contraception from 17.0 percent to 25.6 percent (Table 14).[198] This latter figure may be misleading because many of the women in this group had very infrequent episodes of sexual intercourse. Of more importance is the fact that the percentage of teenagers who had used contraception at the last episode of sexual intercourse had grown from 45.4 percent to 63.5 percent in the five years. This increased use of contraception at the time of last intercourse occurred in teenagers of all ages, with the greatest percentage increase in the younger teenagers (Table 15).[198] Oral contraceptives are the most frequently used method of contraception by sexually experienced teenagers, being used by 31.2 percent in 1976 (Table 16).[198] Use of oral contraceptives increased more than twofold between 1971 and 1976 among all teenagers and in the 15- to 17-year-old age group almost tripled. The percentage of teenagers using IUD's remains small, about 2 percent. Condom usage was very close in popularity to oral contraceptives in 1971, but its use decreased during the five years.

Use of oral contraceptives by teenagers should be encouraged because it is the most effective method of contraception. In women of all ages

TABLE 12.—*Percentage of Teenagers With Premarital Sexual Experience Who Use Contraception**

	All Women	*Women Who Conceived*
Always	26.9	10.9
Sometimes	42.1	23.9
Never	31.0	58.0

*Reproduced by permission from Zelnik and Kantner.[197]

TABLE 13.—*Percentage of Premaritally Pregnant Teenagers and Use of Contraceptives at Time of Conception of Unintended Pregnancies**

	Percent
Intended	28.8
Not intended	71.2
Medical method of contraception	7.4
Nonmedical method of contraception	13.7
No contraception	78.9

*Reproduced by permission from Zelnik and Kantner.[197]

TABLE 14.—*Use (Percent) of Contraception by Sexually Experienced Teenagers in the United States**

	Never	*Sometimes*	*Always*	*Last Time*
1971	17.0	64.6	18.4	45.4
1976	25.6	44.5	30.0	63.5

*Reproduced by permission from Zelnik and Kantner.[198]

TABLE 15—*Percent of Sexually Experienced Never-Married Women Aged 15 to 19 Who Used Contraception During Last Intercourse in 1971 and 1976**

Age	*1976*	*1971*
15-19	63.5	45.4
15	53.8	29.9
16	56.3	38.8
17	61.8	45.2
18	70.3	48.8
19	68.8	55.3

*Reproduced by permission from Zelnik and Kantner.[198]

TABLE 16.—*Percent Distribution of Sexually Experienced Never-Married Women Aged 15 to 19, According to Method Used at Last Intercourse, 1976 and 1971**

	Age		
Method	15-19	15-17	18-19
1976			
Pill	31.2	21.6	42.9
Intrauterine device	2.2	1.3	3.4
Condom	12.6	15.2	9.3
Douche	2.3	2.4	2.3
Withdrawal	10.6	14.9	5.4
Other	4.5	3.0	6.3
None	36.6	41.6	30.4
TOTAL	100.0	100.0	100.0
1971			
Pill	15.1	7.7	23.0
Intrauterine device	0.8	0.2	1.4
Condom	14.4	17.3	11.2
Douche	1.7	2.1	1.3
Withdrawal	10.3	9.4	11.3
Other	2.9	2.4	3.4
None	54.8	60.9	48.4
TOTAL	100.0	100.0	100.0

*Reproduced by permission from Zelnik and Kantner.[198]

the failure rate of oral contraceptives is much less than that of all methods that need to be used at the time of intercourse. Because sexual intercourse is unplanned and frequently multiple in young teenagers, all coitus related methods such as condoms, diaphragms, contraceptive foams or suppositories have a higher failure rate than use of these same methods in older women. Oral contraceptives should be the method of choice in healthy teenage women.

There are some concerns among clinicians about use of oral contraceptives by young teenagers. One concern is that ingestion of these steroids might cause premature closure of the epiphyses. This concern is unwarranted because by the time menarche has occurred the process of epiphyseal closure has already been initiated by endogenous estrogen production, and cannot be accelerated by exogenous sex steroids. Use of exogenous estrogens to prevent growth of potentially tall girls needs to be initiated before the growth spurt, years before the menarche, in order to accelerate the time of epiphyseal closure and decrease the ultimate height.

Another concern expressed is that use of these potent steroids in young teenagers will cause permanent hypothalamic pituitary dysfunction. This concern is also unwarranted provided a girl has already established regular cyclic menses. Use of contraceptive steroids by teenage women does not cause a higher frequency of ovulatory problems after their discontinuation than in older women, provided they both have regular menstrual cycles before starting the steroids. In a retrospective study comparing characteristics of women in whom post-pill amenorrhea developed and those who had secondary amenorrhea unrelated to discontinuing oral contraceptives it was found that the incidence of oligomenorrhea in both groups was similar, about 40 percent.[200] There was no relation between the incidence of post-pill amenorrhea and the age of starting use of oral contraceptives or the duration of their use. The presence of oligomenorrhea before starting use of oral contraceptives is associated with a high rate of post-pill amenorrhea no matter what the age. Therefore, in general, oral contraceptives should not be prescribed to patients with hypothalamic pituitary dysfunction who are not having regular cyclic menses no matter what their age. A girl should have at least three regular spontaneous menses occurring at intervals of less than 35 days before starting oral contraceptives. Teenagers with oligomenorrhea have a low risk of conceiving due to infrequent or absent ovulation, and therefore should be advised to use a barrier method of contraception to avoid the increased possibility of post-pill amenorrhea developing.

Older patients are more concerned about the rare but serious adverse effects associated with oral contraceptive use such as thromboembolism, heart disease and stroke. Because these disorders are extremely rare in teenagers a possible increased risk associated with oral contraceptive use in this age group has not been documented. Most teenagers are not concerned about these problems, but are concerned about the frequent but less serious side effects, such as nausea, weight gain, edema, breast tenderness, breakthrough bleeding, failure of withdrawal bleeding and skin changes—for example, development of or increased severity of acne. Adolescent girls are very conscious of their physical image and are very disturbed about weight gain, edema and skin changes. Development of these changes and other symptoms frequently causes young girls to stop taking oral steroids and will result in unwanted pregnancies. To increase the rate of compliance it is important that patients be informed about the presence of these effects and be assured that many of the minor side effects, such as nausea, breast tenderness and breakthrough bleeding decrease in incidence with increasing duration of oral contraceptive use. Physicians should see patients after three cycles of oral contraceptive treatment to inquire about their symptoms, answer their questions and give reassurance. Most teenagers are healthy and have no medical contraindications to use of oral contraceptives, but the same contraindications that occur in older women, such as systemic metabolic disease, thromboembolism and active liver disease, can be present in teenagers. When medical contraindications exist, alternative methods of contraception should be used.

All combination oral contraceptives are equally effective, and no significant differences in the incidence of breakthrough bleeding or failure of withdrawal bleeding have been shown among the different formulations, although comparative studies have not been done. In deciding which formulation to prescribe initially for teenagers, it is best to use one with less than 50 μg of ethinyl estradiol, as the estrogenic component accounts for most of the undesirable metabolic effects.

Estrogens decrease sebum production, while the androgenic progestogens used in oral contra-

ceptives increase sebum production. Because acne is common in this age group, it is best to avoid formulations with the most androgenic progestogen, norgestrel, because these formulations cause a greater incidence and severity of acne than those with less potent progestogens. Use of the daily progestogens that contain no estrogen avoid many of the estrogenic symptoms such as fluid retention and nausea. However, these formulations have a higher frequency of irregular bleeding and a higher failure rate especially if the pill is not taken exactly at the same time every day. Therefore, it is best not to prescribe daily use of progestogens for teenagers.

The steroids have a long half-life. Therefore, most pregnancies in women using combination pills occur because a patient does not resume taking the pills after the week interval, rather than when a patient forgets to take one or two pills per cycle. To decrease the chance of delaying the interval of no medication for more than one week, it is best to give teenagers formulations containing packages of 28 pills instead of 21. In this way a pill is taken every day and there is less chance to forget to resume medication after an interval without ingestion of pills.

The use of high doses of estrogen postcoitally, which has been termed interception, should not be used for contraception. Interception is an emergency measure that should be used only after a single midcycle coitus and the medication must be started within 72 hours, otherwise the failure rate is high. Because of the high doses of estrogen with their associated side effects, interception should only be used once, and then a continuing method of contraception advised.

The use of IUD's has certain advantages for teenagers. It requires only one act of motivation and it does not have the systemic effects, which occur with oral contraceptives. IUD's also have a high rate of effectiveness, although slightly less than oral contraceptives. Pregnancy rates with the Copper-7 in nulliparous women are in the range of 1 percent to 2 percent. The disadvantages of IUD use are increased and irregular uterine bleeding and pain. Furthermore, there is evidence of about a sevenfold increased rate of pelvic infection in IUD users if they are nulliparous and younger than 25.[201] Most teenagers have more than one sexual partner and there is a greater chance of gonococcal salpingitis developing than in older, married women. As IUD's increase this risk further, use of IUD's by teenagers with multiple sexual partners will increase the incidence of subsequent infertility from tubal damage. At present, until more definitive data are available, it would appear prudent to avoid the use of an IUD in a nulliparous woman unless she has a single sexual partner. The risk of impairing future fertility because of the increased possibility of salpingitis, or ectopic pregnancy if there is contraceptive failure, must be considered when deciding upon use of an IUD in nulliparous women.

If a teenager has medical contraindications to oral contraceptives or does not wish to use them, then a diaphragm can be used with effectiveness provided the patient has sufficient counseling. Condoms also are effective. In one British study the accidental pregnancy rate with condoms in motivated couples was about 2.5 percent at 12 months.[202] In certain urban areas of the United States, the rate of teenage pregnancy decreases when free condoms are distributed widely.

Finally, it is necessary to state that abortion is not the answer to the problem of teenage pregnancy. It is much safer to prevent a pregnancy than to disrupt one after it occurs. Abortion, even when done by vacuum aspiration, is associated with a certain incidence of infection, perforation, intrauterine synechia and subsequent infertility. Also, most teenagers with unwanted pregnancies, do not elect to have an abortion, and if they do, they frequently have the procedure delayed until the gestation is in the second trimester. In addition, many teenagers do not have access to abortion services because of recent restrictive legislation. For these reasons every effort should be made to encourage sexually active teenagers to use effective contraceptives, particularly the orally taken steroids, to decrease the extremely high number of unwanted teenage pregnancies.

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Man's Health: The Past and the Future

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

DR. SMITH:* *At Medical Grand Rounds we usually focus on a single disease or on a new area of technology to summarize in a coherent form our current knowledge of that subject. This discussion will be different. We have asked Professor Thomas McKeown to discuss his concepts of health and disease and the role of physicians in society.*†

DR. MCKEOWN:‡ In this discussion of man's health I would like to (1) outline a concept of the determinants of health and disease, (2) examine past changes in health in relation to these determinants, (3) consider future prospects for control of disease and (4) comment on the role of medicine in general and of clinical medicine in particular in the light of these conclusions.

Because assessment of past achievements and future prospects is likely to be affected considerably by an underlying concept of the determinants of health, I will begin by evaluating certain influences that have led to disease.

- Until the last 300 years (only about one ten-thousandth of his total existence on earth) man was subject to rigorous natural selection. Much earlier, during the nomadic period of human evolution many a conceptus died before birth and many did not survive to reproduce. Man is therefore well adapted to the environment in which he evolved—that of the nomadic period.
- Only a small part of the burden of disease is determined irreversibly at fertilization by genetic or chromosomal abnormalities. Most diseases, including the common ones, result from adverse environmental influences in combination with genetic characteristics that make the development of a particular disease more or less likely but not inevitable.
- The adverse influences are of two kinds: deficiencies and hazards. Of the four essential elements for sustaining life—food, water, oxygen and heat—only food has been seriously deficient. The common hazards have resulted from other living things competing for existence, microorganisms and predators, especially human predators.
- Under the conditions of evolution, basic requirements for health were provision of food and protection from the hazards presented by other living things. Changes in the environment from those conditions under which man evolved

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†This material was given in a modified form as the Osler Lecture, McGill University Faculty of Medicine, Montreal, April 18, 1979.

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create new hazards, resulting from exposure to influences to which man's genes have not adapted.

In light of these conclusions, I will review the determinants of health in the past and, by classifying the residual health problems of developed countries, I will attempt to narrow the area of disagreement about which influences are likely to be important in the future.

The Past

There are many ways in which the history of man's health might be classified. Perhaps the most instructive is by dividing it into three periods—nomadic, agricultural and transitional—each being characterized by profound differences in living conditions and in the nature of its predominant disease problems.

The Nomadic Period

Mankind lived as nomads until relatively recently in human history, dependent on hunting, fishing and gathering fruit for food. Levels of fertility and mortality of man at that time are unknown, and it is questionable whether observations made on the few peoples who have retained a primitive way of life to the present can throw new light on these issues. However, because the population increased very slowly it can be inferred that mortality was high; it took about 3 million years for the human population to reach its first billion (in 1830); the second was added in 100 years, the third in 30 and the fourth in 15 years.

The causes of death can be divided into two broad categories: those for which man was responsible (all forms of homicide, particularly infanticide and tribal war) and those for which he was not directly responsible (food deficiency and injuries arising from hunting and gathering). On the evidence available or likely to become available, it is impossible to assess the relative contributions of these causes of death which, no doubt, varied from one population to another and from time to time. What is evident is that all of these causes are related to the environment and, particularly, to food supplies. For if homicide was common it was probably determined by limitations on resources; and if starvation or disease associated with food deficiency was important, it resulted even more directly from lack of food.

In relation to man's later health history it is important to note that infectious disease is not a common cause of death of wild animals.[1] The same was probably true of early man, for although he doubtless suffered from infections contracted from animal vectors, because he lived in small groups he was unlikely to have experienced many of the diseases which were later prominent, particularly those that are airborne.[2] The propagation and transmission of organisms responsible for these infections require large numbers in close contact; in the case of measles, for example, it has been estimated that a population of about 900,000 is needed to maintain the disease.[3]

I propose that for early man the main causes of sickness and death were food deficiency and hazards from other human beings competing for the same means of existence. The threat presented by microorganisms was relatively less important.

The Agricultural Period

There have been two major changes from the living conditions of early man and both have had profound effects on health and population growth. The first occurred with the transition from a nomadic to a settled way of life about 10,000 years ago; the second is associated with the agricultural and industrial developments of the last three centuries.

The first agricultural revolution brought about an improvement in food supplies that led to a decline of mortality and an increase in numbers. This expansion and aggregation of populations created the conditions required by many microorganisms to flourish, and infection became the predominant cause of death. However, population growth was uncontrolled and numbers increased to the point where resources became marginal again and, thus, the relationship between man and the organisms that caused disease developed while man was, in general, poorly nourished. The relationship was unstable and finely balanced according to the physiologic state of host and parasite: improvement in nutrition would tip the balance in favor of man and deterioration in favor of the parasite. In these circumstances, an increase in food supplies became an essential condition for substantially reducing mortality from infectious disease, and limitation of numbers would have to follow if the reduction was to be permanent.[4]

Thus, the predominant causes of sickness and death in the agricultural period resembled those of the nomadic period in that food deficiency was still critical, but differed in that microorganisms

rather than man himself presented the main threat. This change resulted from the expansion and aggregation of populations—a departure from the conditions under which man had evolved —and was aggravated by defective hygiene.

The Transitional Period

The period since the turn of the 18th century has been one of change, from an agricultural to an industrial way of life. In some countries the transition has been largely accomplished while in others it has scarcely begun. In developed countries there have been profound changes in economic conditions, from poverty to affluence, and in the character of disease problems, from infectious to noncommunicable diseases. In developing countries poverty still prevails and infections remain the most common cause of death. Hence, in the transitional period there is a mix of health problems, both within countries and between countries, and problems that were predominant in the past exist side by side with those that will become more significant in the future.

The first and most important reason for the decline of infectious diseases has been an improvement in nutrition resulting from continued advances in agriculture since the end of the 17th century. Initially, the advances were due to a more effective application of traditional practices and to the introduction of new crops, particularly the potato and maize, rather than to new methods associated with industrialization. However, from the second half of the 19th century agricultural productivity has been greatly increased by mechanization and the use of chemical fertilizers and pesticides.[4]

Second only to nutritional influences in time and, probably, in importance are the improvements in hygiene that have been introduced since the late 19th century. For example, better hygiene is the main reason for the decline of water- and food-borne diseases associated with a fifth of the reduction in mortality from all causes between the mid-19th century and the present in England and Wales. The first advances were in purification of water and disposal of sewage, but from about 1900 they have been greatly extended to include food hygiene, affecting most critically the quality of milk. Control of the environment has, of course, been advanced further in this century by improvements in working and living standards (including such measures as reduction of atmospheric pollution) affecting the community at large as well as domestic conditions.

Except in the case of vaccination against smallpox (associated with less than a 2 percent reduction in the death rate in England and Wales from the mid-19th century to the present) it is unlikely that individual medical care had a significant effect on mortality from infectious diseases before the present century. Between 1900 and 1935 progress was made in controlling infections, such as use of antitoxin for treating diphtheria and salvarsan for syphilis; intravenous fluid replacement therapy for diarrheal diseases; passive immunization against tetanus; improved surgical procedures for treating appendicitis, peritonitis and ear infections, and better obstetric care for the prevention of puerperal fever. But even if these measures were completely responsible for the decline in mortality from these conditions after 1900, which clearly they were not, they would still account for only a small part of the decrease in number of deaths that occurred before 1935. About that time the first powerful chemotherapeutic agents, sulphonamides and, later, antibiotics came into use; both have since been supplemented with improved vaccines. However, use of these early chemotherapeutic agents was not the only reason for the continued fall in mortality. I conclude that immunization and treatment contributed little to reducing mortality from infectious diseases before 1935, and since the practice of registering the cause of death was begun (1838) they have been less important than other influences.[5]

The other major reason for the modern transformation of health has been the change in reproductive behavior which has resulted in a decline in the birth rate in industrialized nations. The importance of this change can hardly be exaggerated. In England and Wales, for example, if the birth rate had continued to rise at its earlier pace the population today would be about 140 rather than 50 million—the effects on health and welfare can be imagined. While initial progress in improved health conditions was due to other influences, the change in reproductive behavior to restrict numbers was an essential complement, without which other advances, such as those associated with the first agricultural revolution 10,000 years earlier, would soon have been reversed.

If we categorize improvements in nutrition and hygiene as environmental factors, the influences most responsible for the decline in mortality and

the increase in life expectancy have been environmental, behavioral and therapeutic. They became effective from the 18th, 19th and 20th centuries, respectively, and the order in time was also the order of their effectiveness.

I conclude that the transitional period has witnessed a change in the common health problems of developed countries, from infectious to noncommunicable diseases. The decline of infections has resulted mainly from reversal of conditions which had made them predominant: deficient food supplies, uncontrolled population growth and poor hygiene. The rise of noncommunicable diseases is due largely to changes in ways of life (from those of the nomadic period) for which man's genes have not adapted.

The Future

The most important question concerning the future of man's health is whether the control of noncommunicable diseases will be achieved mainly by modification of their origins, as in the case of the infectious diseases, or by clinical intervention in disease mechanisms after they have occurred.

Before discussing this issue I will examine the nature of residual diseases that have become predominant as infectious diseases have declined. These diseases can be divided broadly into four categories, distinguished according to the feasibility and means of their control: (1) relatively intractable; (2) preventable, associated with poverty; (3) preventable, associated with affluence, and (4) potentially preventable, but not clearly related to poverty or affluence.

Relatively Intractable

The diseases in this category include the following:

- Genetic diseases. These include the rare single-gene disorders and the more common chromosomal aberrations, most of which are eliminated through spontaneous abortions. Genetic diseases, so defined, are found in less than 0.5 percent of live births and, thus, are not among the common diseases.
- Other diseases determined at fertilization. These are polygenic conditions usually manifested in late life, such as a deterioration in the functioning of eyes and ears.
- Diseases associated with prenatal environmental influences. Most types of mental subnormality and congenital malformations belong in this group. Results of both microscopic and familial studies offer no evidence that such conditions are determined irreversibly at fertilization. However, the deleterious environmental influences affect the embryos early in pregnancy, and most influences are likely to remain unidentified, at least in the foreseeable future.

In designating these diseases as relatively intractable, I am not suggesting that they offer no possibility for prevention or treatment. The withdrawal of thalidomide, the prevention of Rhesus hemolytic disease and the treatment of phenylketonuria are notable examples, quite different in kind, of successful measures in treating certain problems in this category. Nevertheless, I believe that most of these diseases will prove to be relatively intractable, and that even in the third group solutions will seldom result from control of adverse environmental influences (such as that which led to prevention of malformations caused by thalidomide and rubella).

Preventable, Associated With Poverty

Although many people in developed countries are now largely protected from health problems associated with poverty, we should not overlook their continuing importance. In much of the world they still predominate, and even in advanced countries there are sections of the population whose health needs owe more to poverty than to affluence. It is therefore necessary to assess potential advances through wider application of the traditional measures—nutritional, environmental, behavioral and therapeutic—which have led to a decline of infectious diseases.

A useful basis for this assessment is comparing health indices between different populations and between different sections of the same population. For example, in 1970 the differences between continents with the highest (Europe, 71 years) and lowest (Africa, 43) life expectancy at birth was nearly 30 years. Even better figures have been recorded for single countries such as Sweden (72.1 years for men and 77.7 years for women in 1971-1972).

There are also significant differences in health indices between countries at a corresponding stage of development. Figure 1 shows the trend of infant mortality between 1950 and 1975 in six developed countries. At the beginning of this period the highest rate (in Japan) was three times greater than the lowest rate (in Sweden); at the

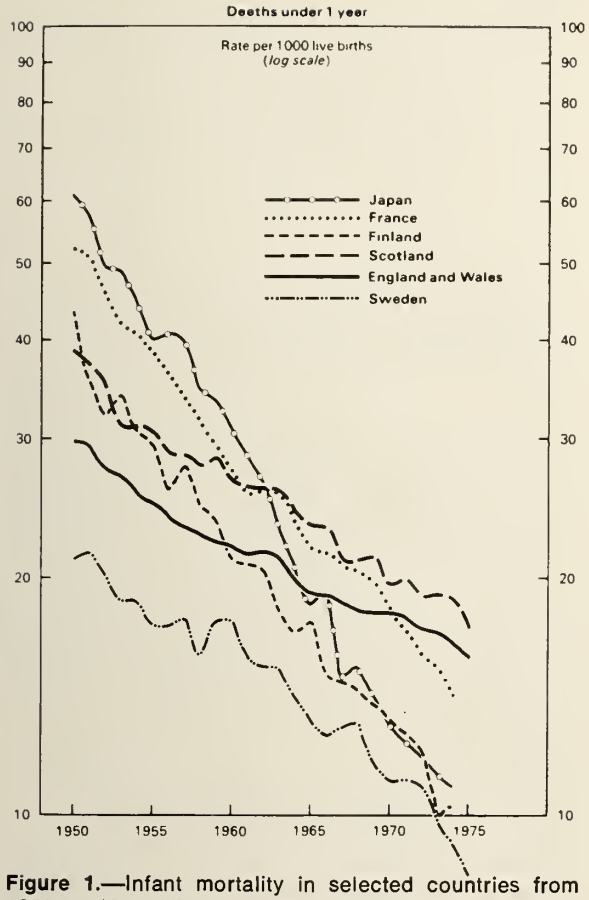

Figure 1.—Infant mortality in selected countries from 1950 to 1975. (From Prevention and Death: Reducing the Risk. London, HMSO, 1977, p 13.)

end of the period the highest rate, in Scotland, was still nearly twice that of Sweden, which was again lowest.

Much can also be learned about health problems from differences in social classes within the same country. In Britain the population is divided for statistical purposes into five classes based on the occupation of the head of the household. Figure 2 shows mortality in 1970-1972 as stillbirths, and for infants under a year, children aged 1 to 14 and adults aged 15 to 64. The relative mortality of the first two groups is expressed as death rates (per thousand total births and per thousand live births, respectively) and of the last two as standardized mortality ratios (SMR). In all four groups there is a striking increase in mortality from the wealthiest class (I) to the poorest (V).

The class differences in mortality are greatest in relation to infective and parasitic diseases and to diseases of the respiratory system. However, the differences are also substantial for malignant neoplasms, diseases of the nervous system and sense organs, diseases of the digestive system, diseases of the genitourinary system, and accidents, poisonings and violence.

Some of the variation in death rates between countries and between social classes within countries can be accounted for in other ways; for

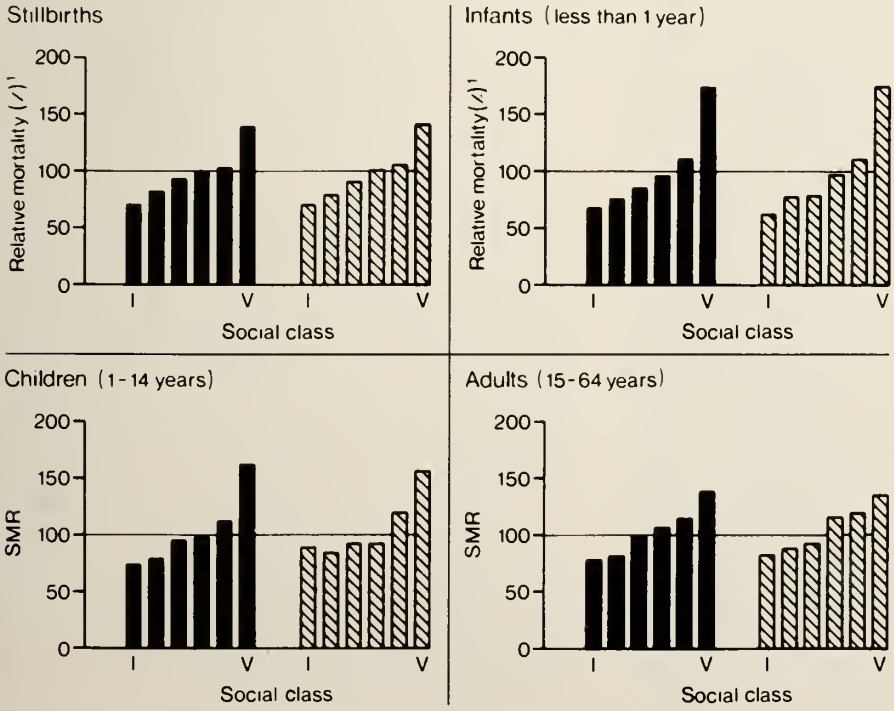

Figure 2.—Mortality by social class and age. Black and hatched bars indicate rates for 1970 and 1972 (SMR = standardized mortality ratios). (From Occupational Mortality, 1970-1972. London, HMSO, 1978, p 196.)

example, by deaths from tropical diseases in developing countries and, less certainly, by differences in behavior between classes. (There is some evidence that smoking is now more common among the poor than among the affluent, and this would increase mortality from malignant neoplasms and certain other causes of death, both infective and noninfective, in the former.) However, I think there is little doubt that differences in health experience are attributable mainly to the direct or indirect effects of poverty, and would be largely eliminated if it were possible to raise the lower standards of living and medical care to those at the highest level.

Preventable, Associated With Affluence

Under this heading I will try to identify diseases determined by behavior associated with affluence. I recognize that not all behavioral influences are associated with affluence (for example, in some poor countries people take opium), and that many health problems of an affluent society are unrelated to individual behavior (for example, the risks of asbestosis to which workers have been exposed). Nevertheless, most of the diseases determined by behavior have become prominent because of affluence and, because their solution depends on modification of personal behavior, it is important to distinguish them from the diseases of poverty which must be solved by society.

Most changes in behavior that have led to disease are comparatively recent. For example, refined foods became widely available in the early 19th century; sedentary living dates mainly from the introduction of mechanized transport, particularly the automobile, and widespread cigarette smoking has occurred only in the last few decades.

Although the relative importance of behavioral and other influences cannot be estimated accurately, it is possible to assess the ill effects of smoking. Table 1 shows the increase in life expectancy of male smokers (25 cigarettes or more per day) and nonsmokers of various ages that has occurred between the mid 19th century and today. For men aged 25, the increase for smokers has been half or less than half of that for nonsmokers. This means that the improvement in life expectancy for mature male smokers has been reduced by at least half. The fact that so large a reduction has been due to a single practice suggests that in advanced countries behavioral influences are now more important than others. And because these behavioral changes have arisen mainly in affluent societies, it seems permissible to conclude that diseases associated with affluence are now predominant. Hence, the order of importance of the major influences on health in industrialized nations differs from that of the past, as well as from that still prevailing in developing countries. That is, personal behavior is now relatively more significant than deficiency in food supplies or environmental hazards.

TABLE 1.—*Statistical Estimates of the Increase in Life Expectancy of Males in the Period 1838-1854 to 1970**

Age (years)	*Nonsmokers (years)*	*Smokers† (years)*
0	31.9	26.0
25	13.2	7.0
35	10.3	4.1
45	7.4	2.1
55	4.6	0.6
65	2.3	0.3

*Based on mortality experiences of (a) British doctors, smokers and nonsmokers and (b) estimates of life expectation of men in England and Wales in 1838-1854 and 1970.

†25 cigarettes or more per day.

Potentially Preventable, but Not Known To Be Associated With Poverty or Affluence

Several diseases remain that do not fit into any of the preceding categories. In principle they are preventable, for there is no reason to believe that they are determined irreversibly at fertilization or that the environmental influences which lead to them are prenatal. However, they have not responded to improved conditions of life or to the advances in medicine that have led to a decline of infectious diseases, and they are not known to have arisen from the changes in behavior made possible by affluence.

They are a heterogeneous group. They include, for example, certain acute respiratory and gastrointestinal infections, many forms of mental illness, and several types of physical diseases including multiple sclerosis, rheumatoid arthritis, most cases of renal disease and a few types of cancers. Many of these conditions are undoubtedly associated with conditions of life, but it is unlikely that they clearly fall into either of the preceding classes.

The division of diseases into four categories suggests the approaches to treatment that are likely to be rewarding in future. Those referred to as relatively intractable (abnormalities determined at fertilization or in utero) are unlikely to be much affected by nutritional, environmental or behavioral changes, and the best prospects lie in

prevention of conception or birth of infants likely to be affected, or in treatment after birth. These measures depend on knowledge obtained through basic research and applied through clinical practice. Diseases in the second class, associated with poverty, can be dealt with best by the use of methods that have led to the decline of infections, such as improved nutrition, reduction of exposure, immunization and early treatment. Control of diseases associated with personal behavior made possible by affluence requires changes in behavior, a task which both individual persons and society must share.

Those conditions which seem preventable in theory, but which have neither responded to improvements in the standard of living nor appear determined by personal behavior, may cause the greatest controversy regarding the best methods of treatment. For some disorders (such as those resulting from occupational hazards), success is most likely to come from control of their origins; in others (such as the common cold) there is more hope from intervention in disease mechanisms because we are unlikely to eliminate the aggregation of populations which provides the basis for transmitting these infections. But in many diseases where neither of these approaches seems clearly the more promising, the prudent course is to investigate them both.

Medical Responsibilities

If health is determined essentially by nutrition, personal behavior and the quality of the environment, then it is clearly desirable to reconsider the role and responsibilities of medicine in relation to such influences. Indeed, this has already been done, and some have suggested that these influences are not the concern of physicians, whose work should be limited to the care and, where possible, the cure of individual patients.[6,7] From this conclusion it would follow that behavioral and environmental problems, whose solutions depend largely on economic and social measures addressed to populations, lie outside the scope of medical education.[8] It is also implied that these concerns are not among the wider responsibilities of medicine.

Because I disagree with this position I will examine three of the arguments on which it is based: (1) that for the solution of disease problems we must rely on a biomedical approach; (2) that medicine, which is concerned primarily with individual persons, has little to contribute to the understanding and control of aggregate problems, and (3) that preoccupation with such problems threatens medicine's essential function, which is to care for the sick.

First, it has been said that an approach based on laboratory science and clinical medicine offers the only hope for the solution of the major medical ills that afflict mankind.[8] This statement is patently untrue, unless the term "major medical ills" is restricted to a well-defined group of diseases. Certainly, there is one category—diseases determined at fertilization or in utero—in which only this approach offers much prospect of success, and with many diseases in the fourth group (discussed above) it is as promising as any other. But the major health problems today are largely determined by behavior in developed countries and by poverty in the world as a whole, and only in the remote future, when these problems may have been solved, might it be true to say that the biomedical approach offers the chief hope for a solution of the ills that remain. That is, if the diseases associated with poverty or a departure from the conditions under which man evolved were eliminated by control of their origins, then the residual problems would be those that must be tackled through knowledge of their mechanisms.

The second suggestion—that medicine has little to contribute to the solution of aggregate problems—should be considered in relation to both research and practice. If this view were accepted, there is little doubt that medical research would be increasingly polarized towards the study of disease mechanisms, with serious risk of neglecting disease origins. The scope of enquiry is greatly broadened when it is illuminated by clinical experience, and many examples could be cited to support the conclusion that medical interest is essential for indentification of environmental and behavioral influences on health. It was a doctor's experience of cholera that led to investigation of water supplies, clinical observations of malformed patients that resulted in recognition of the teratogenic effects of thalidomide and rubella, and a surgeon's awareness of the different disease patterns between Africans and Europeans that drew attention to the relationship of refinement of food to intestinal disease. Such advances are unlikely to come from a profession dedicated exclusively to the prevention and treatment of disease in individual patients.

When adverse influences have been identified,

their control is largely in the hands of nonmedical people. Nevertheless, I believe that medical specialists in nutritional and environmental medicine are needed, and they can hardly emerge if these subjects are excluded from medical education. Medical involvement in modification of behavior also seems desirable. It would be unsatisfactory if the major determinants of health in advanced countries were left entirely to people with little knowledge of the diseases concerned, or if approaches to controlling the subtle influences that shape health-related behavior were carried out by such ineffective means as posters and public exhortations.

But whatever the decisions about appropriate medical contributions to public activities related to nutrition, environment and behavior, physicians have an inescapable responsibility regarding behavior that affects the health of their patients. If the diet of a diabetic and the exercise of a sedentary worker who has had a coronary thrombosis are matters for the physician, so too are the smoking habits of an adolescent, if prevention as well as treatment of disease in individual persons is an accepted goal. There are many circumstances in which a doctor can say accurately: I can do more for this patient by influencing his behavior than by any treatment that can be prescribed (a possibility not considered by a general practitioner who was overheard by a medical student to say, "Don't worry about your smoking, just keep on with the tablets").

Before examining the suggestion that however desirable medical interest in the aggregate problems affecting health might be, it would prejudice a physician's primary responsibility for the care of individual patients, I must remove some possible sources of misunderstanding. First, I do not question that the care of the sick is a physician's primary responsibility and that medical education should be directed largely to that end. Second, the conclusion that the main determinants of health are likely in the future, as in the past, to lie outside the medical care system in no way diminishes the importance of the clinical function. When people are ill they want all that is possible to be done for them, and small benefits are welcome when larger ones are not available. Nor does an inability to reverse the course of established disease reduce the importance of the pastoral or samaritan role of the doctor—in some ways it enhances it.

However, the belief that wider responsibilities are incompatible with personal care results from equating the role of medicine as an institution with that of clinical practice. Certainly, a physician who treats sick people cannot be expected to deal with national food policies, changes in the environment and public attempts to modify behavior, although an understanding of these influences on health seems as relevant to his work as knowledge of the chemistry of the drugs he administers. Medicine as an institution should be concerned with such matters and with many others that lie outside the clinical role. I suggest that medicine's responsibilities might be defined as follows: To assist us to come safely into the world and comfortably out of it, and during life to protect the well and care for the sick and disabled.[5] The protection of the well and the care of the sick (in some of its aspects) cannot be achieved through services directed exclusively to individual patients.

I see no reason why additional responsibilities cannot be accepted without prejudice to the primary clinical function. A knowledge of the origins of disease should be included in medical education, for it is as basic to medicine as an understanding of natural selection is to biology; additional instruction can be provided through electives for those who wish to specialize in nutritional, behavioral and environmental medicine. I believe that medical research needs to be guided by an analysis of disease problems such as that outlined above, and would be crippled if investigation of disease origins were strictly separated from that of disease mechanisms. It is fortunate that such a demarcation was not imposed on research on infectious diseases during the past century.

In health services as well there would be many disadvantages in limiting the role of medicine to clinical practice. There would be no profession concerned comprehensively with health matters, and the division between professions dealing with the prevention and treatment of disease would be regrettable. One of the unfortunate features of contemporary professional organizations (societies, associations, colleges, faculties, and so forth) is their emphasis on sectional or regional interests. Collectively, they provide no forum for consideration of the larger issues that should be the concern of medicine as an institution.

Finally, I wish to consider briefly a few implications for clinical medicine of the conclusions drawn concerning the determinants of health. One is the need for a more critical appraisal of the

effectiveness and efficiency of medical procedures for which Cochrane has argued so persuasively.[9] Another is acceptance of responsibility for all aspects of the care of the sick, particularly that of patients—such as the mentally ill and retarded and many of the elderly—whose treatment offers no scope for active measures of investigation or cure. Finally, there is a need for increased attention to the care of patients with terminal illnesses.

There have been some interesting reactions to the conclusion that today clinical intervention cannot be expected to have much impact on the common indices of health. For example, it has been suggested that the emphasis should be switched from increasing man's life span to improving its quality; that drugs "for the relief of symptoms rather than etiology is a goal truly worthy of intensive study and originally was the only realistic goal of medicine."[10]

These views are based on the recognition that the therapeutic advances of the last few decades have had little effect on death rates, and that in developed countries we are approaching the "normal" life span which medicine cannot be expected to extend. It is possible to accept both observations without agreeing that cure, in the full sense, is no longer a realistic aim. A patient with a life-threatening illness—such as malignant hypertension, multiple sclerosis, leukemia or nephritis—wishes above all to be restored to a life of normal duration, and this goal deserves equal attention as projects to improve the quality of life. This aim is not invalidated because extension of life in such diseases cannot have much effect on either national death rates from all causes or on life expectancy at birth, as the number of people affected by these diseases is small in relation to the total population, and many illnesses occur late in life when the possible addition of years is limited. Success in prolonging life in patients with specific diseases should be assessed in relation to the number affected by them rather than to the general population.

It has also been said that the common indices of health are inappropriate to the work of a physician, that "tests of the 'outcome' which are obtainable in the public health system are seldom helpful in the personal encounter-physician system."[11] This conclusion is drawn largely from recognition of two difficulties, one of assessing the work of individual physicians and the other of separating the therapeutic aspects from other facets of care, sometimes referred to as the pastoral or samaritan role.

Recognizing these difficulties, I nevertheless think it is important to examine carefully the different components of clinical service before concluding that indices of effectiveness are inappropriate to them. All aspects of service cannot be assessed quantitatively, nor can they be dissociated from one another in the day-to-day delivery of care. But sooner rather than later, rising costs will make it necessary to introduce cost benefit evaluation, and to accomplish this it will be essential to classify clinical services according to the nature of the tasks involved.

Considering that one of the reasons given for not assessing outcome is the importance of the samaritan role, it is remarkable that the samaritan role itself is often prejudiced by lack of evidence of effectiveness. For when clinical procedures are not evaluated scientifically they are evaluated intuitively; each practitioner makes up his own mind about the usefulness of, say, radical mastectomy, tonsillectomy, cervical cytologic procedures or prolonged rest after myocardial infarction. The benefits of intervention and the associated technology are frequently overestimated and this may result in the neglect of patients after the acute phase of illness, or of those persons (such as the mentally handicapped) who provide no scope for active measures. In a recent book, *The Role of Medicine,* I have attempted an analysis of the tasks of clinical medicine under five headings—reassurance, treatment of an acute emergency, cure, care and comfort—and concluded that tests of effectiveness are appropriate in two of them (the second and third).[5]

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Important Advances in Clinical Medicine

Epitomes of Progress — Pediatrics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in pediatrics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Honey, Infant Botulism and the Sudden Infant Death Syndrome

INFANT BOTULISM is the infectious disease that results when spores of *Clostridium botulinum* germinate and colonize the intestines in infants and then produce botulinal toxin in vivo. In contrast, food-borne botulism is an intoxication that affects older children and adults, and which results from the ingestion of botulinal toxin that has been produced by *C botulinum* growing in an improperly preserved food. Although infant botulism was recognized as a distinct clinical and epidemiologic entity only in late 1976, already more than 100 cases have been identified in 21 states, as well as in England and in Australia.

Because most infectious diseases have a spectrum of severity, the recognition that infant botulism resulted from an intestinal infection suggested that it likewise would display variation in severity. Because botulinal toxin is the most potent poison known (about 10^{-9} mg per kg of body weight given intravenously being a lethal amount for man), it appeared possible that rapid in vivo production of botulinal toxin might in some infants lead to sudden death if upper airway obstruction or apnea resulted from flaccidity of airway and respiratory muscles. Consequently, autopsy specimens from 280 California infants were specially studied. *Clostridium botulinum* toxin or organism (or both) were detected in ten of the infants, all of whom died suddenly and unexpectedly. The case histories and autopsy findings in these ten cases were indistinguishable from those of typical cases of sudden infant death syndrome (SIDS). Neither *C botulinum* organisms nor toxin were found in 68 infants who died of known causes. The actual proportion of SIDS that may be due to infant botulism has not been finally established. Interestingly, the characteristic age distribution of SIDS—considered to be unique to this enigma—is virtually identical to that of infant botulism.

Where does honey fit in all of this? Like other agricultural products, honey contains *C botulinum* spores. Of more than 300 food and drug items tested in association with California cases of infant botulism, *C botulinum* was found only in honey. In every instance in which *C botulinum* was isolated from the honey actually fed to an infant, the toxin serotype (A or B) of the *C botulinum* organisms in the honey matched the

serotype of the patient's illness. By food history, honey exposure was found to be a significant risk factor for type B infant botulism. Worldwide, 35 percent of babies with infant botulism were fed honey (but it is important to note that 65 percent were not). In a separate survey, *C botulinum* was found in retail and producer honey samples from nine widely separated states, and these samples were not associated with cases of infant botulism. Clearly, contamination of honey with spores occurs before the honey reaches the home. Using current laboratory methods, about 10 percent of honey has been found to contain *C botulinum*.

There is insufficient information with which to decide whether or not honey may play a role in SIDS. In none of the ten rapidly fatal cases of infant botulism diagnosed by examination of autopsy specimens had the infants been fed honey. Of the three infants that died from infant botulism after admission to hospital, two had been fed honey and one had not.

Honey is the one identified, avoidable source of *C botulinum* spores for susceptible infants. Because honey is not essential for infant nourishment, it may be omitted from infants' diet, and should be. As 65 percent of cases had no honey exposure, elimination of honey from infant foods will not eradicate all infant botulism. However, omission of honey from infants' diet is the first step—and at present the only practical preventive measure for infant botulism that parents and health care providers can practice. The safety of honey for older persons with normal intestinal physiology remains unquestioned.

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Haemophilus influenzae: Secondary Spread

REPORTS OF THE SPREAD of serious infections due to *Haemophilus influenzae* type B within families and at day-care centers suggest that young children are at increased risk of contracting serious disease due to this organism within one month of illness in a close contact situation. It has been well established that the risk of secondary cases among household contacts of patients with meningococcemia or meningococcal meningitis is approximately three per 1,000. Recently, similar estimates of the frequency of secondary illness in household and day-care center contacts of children with serious disease due to *H influenzae* have become available.

Filice and co-workers have estimated the risk of serious secondary illness to be 0.4 percent in all household contacts of patients with *H influenzae* meningitis. They report a secondary attack rate for contacts two years of age and younger of 4.9 percent. A larger prospective study conducted by the Center for Disease Control involved a one-month follow-up of all household contacts of 1,147 cases of *H influenzae* meningitis. Nine cases of serious disease due to *H influenzae* were detected, all in children less than 6 years of age. The age-specific risk of secondary disease was as follows: younger than 1 year, 5.0 percent; 1 year, 1.4 percent; 2 to 3 years, 1.5 percent; 4 to 5 years, 0.1 percent.

Ward and co-workers have reported similar findings in a day-care facility. During an eight-day period, serious disease due to *H influenzae* developed in three of 75 children, 5 months to 6 years of age. All three patients were less than 1 year of age. The attack rate at the day-care center was 4 percent for all children, and 25 percent for infants. Approximately 5 percent of the children at the day-care center were found to be nasopharyngeal carriers of *H influenzae*. All staff were culture negative. Three of five siblings and two of ten parents of infected children had positive nasopharyngeal cultures.

These studies suggest that young children are at increased risk of contracting serious diseases due to *H influenzae* within the month after onset of illness in close contacts. Therefore, prophylaxis of infants and children less than 6 years of age should be considered. Rifampin, cotrimoxazole and ampicillin have been suggested as prophylactic agents. Only limited data are available on the efficacy of these agents, and to date only rifampin appears to be effective in eradicating nasopharyngeal carriage. The dosage of rifampin is 10 mg per kg of body weight per day (not to exceed 600 mg per day) for four days. Adverse effects are unusual; they include gastrointestinal disturbances, headache, drowsiness, ataxia and hypersensitivity reactions. Hepatic, hematologic and renal abnormalities are usually transient. More

studies are needed before recommendations regarding prophylaxis can be made. Prophylaxis of contacts more than 6 years of age is probably not justified.

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Splenic Trauma in Children

RUPTURE OF THE SPLEEN is the most common intra-abdominal injury occurring in children following blunt trauma. Emergency laparotomy and splenectomy are customarily carried out. However, an increasing awareness of the syndrome of overwhelming postsplenectomy infection (OPSI) has caused many pediatricians and surgeons to reevaluate this form of treatment.

While the incidence of sepsis following splenectomy secondary to trauma is low, the associated mortality is 58 times greater than that reported for similar infections in the general population. Classically, these infections occur abruptly with a florid bacteremia and a high incidence of disseminated intravascular coagulation. Death, frequently occurring within hours of onset, is seen in 80 percent of cases. *Diplococcus pneumoniae* is the causative organism in most instances, followed by *Haemophilus influenzae* and *Neisseria meningitidis*. Children less than 5 years of age are usually affected and, in most cases, OPSI is seen within two years following splenectomy. Several patients, however, have been adolescents at the time of splenectomy and infections have occurred as late as 15 years following splenectomy.

Due to the high mortality associated with OPSI, penicillin prophylaxis for up to two years following splenectomy has been advocated, but efficacy of this regimen has not been proved. Pneumococcal vaccine is now available for clinical use; however, this vaccine is only effective against 80 percent of pneumococcal infections and is not recommended for children less than 2 years old. There are reported instances of pneumococcal sepsis in postsplenectomized persons who have received pneumococcal vaccine that includes the type of organism responsible for the infection.

Alternative methods of management have recently been proposed for children with traumatic rupture of the spleen because of the possible risk of OPSI. New surgical techniques have been developed that make it possible for the injured spleen to be repaired and preserved. Several clinical reports have been published showing the feasibility and safety of this form of treatment. Another approach is nonoperative observation after confirming the diagnosis of an isolated splenic rupture by either splenic scan or arteriogram. In such instances, the children are admitted to an intensive care facility where their conditions can be carefully monitored. Surgical operation is not done if a patient's hematocrit stabilizes within 48 hours and the need for transfusion does not exceed a third of the patient's blood volume. Twenty patients have been treated in this manner at the Children's Hospital Medical Center in Boston. Splenectomy was not required in any patient and there were no late sequelae.

An interesting article by Pearson and co-workers suggests that splenosis following traumatic splenectomy is more common than previously thought and may protect against OPSI. In 13 of 22 children there was splenic activity one to eight years following traumatic splenectomy. Splenic scans done on five children showed significant extrahepatic uptake of radionuclide. The protective effect of splenosis is open to question, however, because autopsies in several fatal cases of OPSI following traumatic splenectomy have shown significant splenosis or accessory spleens. This finding supports the experimental evidence that the quantity of splenic tissue and the vascular supply to this tissue are important factors in the prevention of pneumococcal sepsis. Several studies also indicate certain specific splenic functions act independently of others. Consequently, the ability of splenic tissue to remove degenerate red cells does not necessarily correlate with its ability to prevent pneumococcal sepsis.

Based on the above discussion, the following recommendations can be made. A child in whom a splenectomy has been done should be given a pneumococcal vaccine. Penicillin prophylaxis should probably be instituted as well and continued for at least two years following splenectomy. While the efficacy of penicillin prophylaxis has not been well documented, many physicians recommend lifelong treatment with penicillin in children after splenectomy. When an emergency laparotomy is carried out in a child and an isolated splenic injury found, splenic repair should

be attempted if technically feasible. Observation without immediate laparotomy can be considered in certain cases of blunt abdominal trauma in children after confirming an isolated splenic injury by splenic scan or arteriogram. Adequate pediatric intensive care facilities must be available so that the child can be constantly monitored.

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Acetaminophen Toxicity

TOXICITY FROM OVERDOSES of acetaminophen has become a well-recognized entity during the past few years. Fortunately, basic scientific studies have provided sufficient data to design a rational and effective treatment. The National Multiclinic Open Study for evaluation of N-acetylcysteine has provided more data than expected in the more than 1,500 cases collected during the past two years. Some observations are now possible about the incidence, diagnosis and treatment of acetaminophen overdose.

Ingestion of acetaminophen in children even when there are toxic blood levels produces rare hepatotoxic effects. While a few cases in young children have resulted in very high serum glutamic oxaloacetic transaminase (SGOT) levels, the outcome has been almost universally satisfactory. In one case with a SGOT level as high as 20,000 IU per liter, the patient left the hospital with no toxic sequelae on day 7. Acetaminophen then produces a very rapid rise in SGOT with rapid resolution of the toxic process.

In 18 percent to 25 percent of persons older than 12 years, toxic blood levels will be found and some alteration of hepatic enzymes detected. Correlation between history and toxicity is totally lacking and the only way to determine whether a patient has potential for hepatotoxicity is to determine blood levels four or more hours after ingestion. Mortality has been less than 0.4 percent and in fatal cases the patients had generally sought medical attention more than 24 hours after ingestion. Morbidity is most common in those patients seen by a physician between 16 and 24 hours after ingestion and is rare in those patients presenting up to 16 hours after ingestion. Treatment has been provided for all patients up to 24 hours after ingestion.

Even in those patients with SGOT levels above 1,000 IU per liter, no residual toxicity has ever been found. Liver biopsies at three months and a year after hepatotoxicity show no abnormalities.

There has been a major misconception about chronic toxicity. Salicylates, for example, have cumulative kinetics and therefore chronic salicylism may result following therapeutic use of the drug. Acetaminophen, on the other hand, does not have cumulative kinetics and cannot continue to rise in concentration unless the dose is continuously raised. This chronic toxicity is reduced in persons taking an excessive amount of acetaminophen over a period sufficient to deplete hepatic gluthethione as in an overdose.

The National Multiclinic Open Study was not a controlled study in the usual sense because of a number of ethical considerations. In using historical controls, even with the related statistical problems, clear-cut advantages in reduction of peak SGOT levels were obtained. The drug is still on an Investigation New Drug license and permission to use the drug, as well as the method, can be obtained by calling 800-525-6115.

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Human Breast Milk—Storage and Safety Considerations: Protective Effects

DEBATE REGARDING the benefits of human milk in infants of low-birth weight continues. The ease of digestibility, the presence of host resistance factors and the decreased incidence of sensitization with foreign protein are the reasons that human milk is being used with increased frequency in intensive care nurseries. Currently, few data are available on the effects of collection, processing and storage of various components of the milk. Human milk contains large quantities of macrophages and lymphocytes; however, these cells cling to the sides of glass containers, thus reducing the quantity available for the infant. Slow freezing, lyophilization, pasteurization (63° C for 30 minutes) and sterilization (100°C for 20

minutes), destroy the leukocytes. Rapid freezing and maintenance of the milk at −70°C will not destroy the cells if the milk is appropriately thawed, but few nurseries have the facilities for rapid freezing.

Freezing and lyophilization greatly decrease the concentration of IgG and IgM, but have little effect on the concentration and function of IgA, which is present in great quantities in human milk. Pasteurization decreases the concentrations of IgG and IgM to a lesser extent, but to a greater extent with IgA than does freezing and lyophilization. Sterilization inactivates all immunoglobulins, as well as all lipases contained in human milk—which are necessary for the rapid digestion and absorption of fat in the milk.

The ideal method of collecting human milk consists of the mother carefully washing her hands and cleansing her breasts, and manually expressing her milk rather than using a mechanical device. After the first 5 ml is discarded, the milk is collected in a plastic container and given directly to the infant. The milk may be refrigerated for as long as 48 hours, but it is preferable to use it within four hours. If there is a delay, the milk should be frozen or lyophilized. The milk should also be cultured intermittently to evaluate the techniques of collecting and processing.

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The Down Syndrome

THE DOWN SYNDROME is one of the most common birth defects, occurring in one in every 1,000 newborn infants in all racial groups. More than 95 percent of the affected infants have trisomy 21; the remainder have either translocation of the extra chromosome 21 to another chromosome or another abnormality such as mosaicism. Using the new chromosome-banding techniques, it has been shown that about 25 percent of the infants with trisomy 21 have derived the extra chromosome from the father, but this is unrelated to the age of the father. Trisomy 21 does show a correlation with maternal age; an older mother is much more likely to have an affected child than a younger mother. Because fewer older women are having children now than in the past, most (80 percent) of the infants with trisomy 21 are being born to women younger than 35 years old. Prenatal diagnosis by amniocentesis should be discussed as an option for each pregnant woman 35 or older. Another recent finding made possible by banded karyotypes is the determination that only the distal long arm of chromosome 21 needs to be present in triplicate, not the entire chromosome 21, to cause the infant to have the phenotypic features of the Down syndrome.

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PCP Update

ABUSE OF PHENCYCLIDINE (PCP) and its related overdose has become widespread in the United States, particularly in the 12 to 21 year age group. It is essential that pediatricians become familiar with the newly described clinical presentations and treatment for this common emergency problem.

Since PCP's first appearance in 1967, the patterns of use, abuse and clinical presentation have increased significantly. The National Center on Drug Abuse estimates that approximately 6 percent of persons between 12 and 17 years old and 14 percent of those 18 to 25 have used PCP. Its use as a drug of choice taken daily has increased dramatically and it is now one of the most popular of illicit drugs (7 million users in the United States).

Although the drug can be injected, ingested, sniffed or smoked, the pattern of use has changed from ingestion of the drug to smoking it by sprinkling it on some leafy mixture.

Most experienced users have become skilled at controlling their dose so that the effects are not serious enough to warrant medical attention. Frequent overdoses do occur, however, because the potency in street drugs and the tolerance of the drug by patients vary greatly.

Depending on the dose and the stage at which the person is seen, PCP overdose can produce an enormous array of symptoms. These can range from agitation, uncoordination, muscle rigidity,

nystagmus, loss of pain sensation and blank staring when the drug is taken in low doses to prolonged coma, hypersalivation, hypertension, convulsions, opisthotonos and death in high doses. Extremely disturbing behavioral effects are also seen both in low-dose toxicity and during recovery from severe overdoses. They may be very bizarre, paranoid and violent and place the patient at great risk for accidents (falling from high places, drowning, assaults, homicide). Most phencyclidine-associated deaths have occurred in this manner.

Some of these behavioral manifestations or a classic schizophrenic syndrome may also occur with chronic low-dose use or as a delayed phenomenon weeks later after a single dose. Young patients presenting with schizophrenia without a previous history of psychiatric disturbance should be evaluated for PCP toxicity.

Unfortunately, measurable quantities of PCP in blood and urine are often not found in these patients although PCP is present in the brain as a result of lipid storage and reabsorption from the stomach.

The current approach to treatment developed by Alan Done at Children's Hospital of Michigan is based on the principles of ion trapping of weak bases and acids. PCP, a base, will be trapped in an acid medium. Because cells are more acid than extracellular fluid, PCP is trapped in cells. By acidifying the patient, PCP can be shifted from the cells (such as in the brain) to the extracellular fluid and excreted in the urine.

Acidification can be accomplished by administering the following:

- Ammonium chloride, 2.75 mEq per kg of body weight every six hours by nasogastric tube (carry out continuous gastric suction between doses to remove recirculated PCP and adjust gastric losses by giving appropriate fluids intravenously);
- Ammonium chloride intravenously as 1 percent solution in saline to bring blood pH intermittently to 7.3 and urine to less than 5;
- Cranberry juice and 2 grams of ascorbic acid orally four times a day for mild symptoms or low-dose toxicity.

Frequent monitoring of pH and serum osmolality is essential.

In addition, furosemide (Lasix), 20 to 40 mg given intramuscularly or intravenuously, should be administered when urine pH falls below 5. Other symptomatic treatment consists of appropriate airway management and assisted ventilation; diazoxide, 2 to 5 mg per kg of body weight given intravenously for hypertension; diazipam (Valium), 2 to 6 per sq meter given intravenously for seizures; haloperidol (Haldol) for severe psychosis.

Because these patients are difficult to manage, physicians should contact their regional poison center and its medical toxicologist for consultation or transfer.

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Use of Pneumococcal Vaccine

FULMINANT SEPSIS and meningitis caused by *Streptococcus pneumoniae* occur with increased frequency in children with sickle-cell anemia and nephrotic syndrome, and children after splenectomy. Age and the reason for removal of the spleen correlate with the incidence of overwhelming sepsis. After splenectomy, this risk is lowest (but real) in normal children in whom the procedure has been done because of trauma and highest in 4-year-old or younger children and those with hematological disorders affecting the reticuloendothelial system. Children with biliary atresia and cirrhosis are also at high risk for fatal infections of sudden onset, as are neutropenic patients. In addition, at least 20 percent of normal children have one or more attacks of otitis media caused by *S pneumoniae*.

The pneumococcal vaccine which has recently been released for use contains 14 serotypes. Tentative decisions must be made as to the proper role of this vaccine in the care of children. The vaccine contains the following types according to the American typing system: 1-4, 6, 8, 9, 12, 14, 19, 23, 25, 51 and 56. Because Danish typing sera are more readily available, the Danish nomenclature is used in most reports which specify the serotypes causing infection in children. Danish serotypes 7 and 18 correspond to American types 51 and 56.

Adults and children differ with regard to the frequency of infections with specific serotypes. The vaccine stimulates an antibody response only to the capsular polysaccharides which it contains. Studies suggest that 85 percent of pneumococcal bacteremia in children is caused by serotypes contained in the present vaccine. Two serotypes, 11 and 15, which commonly colonize children are

not included in the vaccine. On the basis of studies in adults, the vaccine is expected to reduce the incidence of serious infections by 82 percent to the serotypes included in the vaccine. The incidence of pneumococcal infections in immunized children would, therefore, be expected to be reduced by about 70 percent.

The present vaccine which is manufactured by Merck Sharp & Dohme is not the same vaccine as that used by Ammann and co-workers in their study of the efficacy of pneumococcal vaccine in children with sickle-cell anemia. The vaccine used in their study contained fewer serotypes and was manufactured by Eli Lilly and Company. The mean age of the immunized children in the study was 11.3±5.9 years. The antibody response to pneumococcal vaccine is poor in children younger than 2 years old, and the clinical efficacy of the vaccine in children 2 to 4 years old has not yet been evaluated. Most fatal infections in children with sickle-cell anemia occur in children younger than 5. The frequency of infection in children after splenectomy probably lessens as the child becomes older. This, of course, also corresponds to an increase in the interval following splenectomy. However, overwhelming sepsis has been reported in normal adults as long as 15 years after splenectomy has been carried out because of trauma.

After splenectomy because of trauma, spherocytosis or idiopathic thrombocytopenia, patients respond normally to the vaccine. Children with the nephrotic syndrome respond even when in relapse or on a regimen of prednisone. The serological response to the vaccine is poor in patients treated for Hodgkin disease and in young children. Serious infections due to serotypes included in the vaccine have occurred in young, immunized children with sickle-cell disease.

Results of trials of penicillin prophylaxis are not yet available and a dose is not well established. Continuous penicillin prophylaxis in patients with normal life expectancies, such as those in whom splenectomy has been done because of trauma, is not practical. In addition, prolonged prophylaxis might interfere with the development of natural resistance and defer serious infections to adulthood.

A reasonable approach to prophylaxis against overwhelming pneumococcal infections in children would be to administer penicillin up to the age of 5 and to immunize at 5 years of age. Following immunization, children whose underlying disease places them at extremely high risk of infection should continue to receive penicillin. Children at relatively low risk of infection, such as after splenectomy for trauma, could be managed without penicillin. In such cases, however, penicillin should be kept in the patient's house and be given empirically if the patient's temperature exceeds 39°C (102.2°F) or the patient should be seen by a physician if such a fever occurs. When compliance is poor, immunization of children younger than 5 years old may provide valuable, although possibly incomplete, protection.

Regular use of the vaccine in patients with congenital heart disease and cystic fibrosis to prevent pneumonia, and in normal children to prevent otitis media should be deferred until the efficacy of the vaccine in decreasing recurrent infection is known.

Widespread interest in the vaccine will continue because the appearance of penicillin-resistant pneumococci in the United States raises concerns about the need for new means of control of pneumococcal infections.

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Valproic Acid

VALPROIC ACID, introduced in Europe in 1967, became available in the United States in 1978. The drug represents a substantial clinical advance in the control of epilepsy in children. It is useful as a primary drug in petit mal (simple absence) and minor motor (akinetic) epilepsy and as an additive medication in generalized (tonic-clonic) seizures. It is marketed as Depakene in 250 mg capsules (valproic acid) and as a 250 mg per 5 ml suspension (sodium valproate).

Valproic acid is most useful in controlling minor motor and myoclonic seizure activity. It is the initial drug of choice in children with myoclonic seizures, although it is relatively poor in controlling infantile spasms. It is of particular benefit to teenagers with intractable petit mal seizures. Despite its success in petit mal, ethosuximide (Zarontin) alone or in combination with acetazolamide (Diamox) is used before trial with

valproic acid in patients with the recent onset of uncomplicated petit mal. Despite original reports of poor control in patients with generalized seizures, valproic acid alone may be successful in children occasionally—but usually it is given in combination with phenytoin (Dilantin), phenobarbital or carbamazepine (Tegretol) in reducing or preventing seizure activity in difficult patients. It is usually ineffective in suppressing psychomotor (complex partial) seizure activity and in simple febrile seizures.

Recommended dosage is 15 to 60 mg per kg of body weight per day given in three divided doses because its serum half-life is approximately eight hours. In previously unmanageable patients, we frequently start at 30 mg per kg and rarely exceed 60 mg per kg. Therapeutic blood levels are achieved three days after initiating valproic acid therapy, so weekly medication changes can be used to titrate seizure activity. The therapeutic serum level is 50 to 100 μg per ml.

Although relatively free of side effects, fatal hepatitis due to valproic acid has been reported. Children may have abdominal upset which usually can be minimized by taking the medication with meals; however, anorexia, vomiting and lethargy will occasionally force discontinuing the drug. Hair loss may occur upon initiating the drug, but is usually transient. Thrombocytopenia and leukopenia have also been noted. Caution should be exercised when valproic acid is added to other anticonvulsants because it may both depress serum levels of phenytoin and elevate serum levels of phenobarbital.

When valproic acid is used in combination with other anticonvulsants, serum levels of all anticonvulsants should be monitored after several weeks. Surveillance of children receiving valproic acid should include a complete blood and platelet count as well as a serum glutamic oxaloacetic transaminase (SGOT) study before, two weeks after introducing the drug and at monthly intervals for six months. Elevations of SGOT should be studied with a full hepatic panel including prothrombin time. After six months on the medication, reassessment every three months should be sufficient.

For a number of previously poorly controlled patients, valproic acid is a safe and highly effective new anticonvulsant. However, physicians prescribing the drug should be familiar with its rare but potentially serious reactions.

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EDITORIALS

Utah Joins the *WJM* Family

THE WESTERN JOURNAL OF MEDICINE welcomes the Utah State Medical Association to the growing family of western state medical associations which have recognized *WJM* as their official journal. This was accomplished by an action of the USMA House of Delegates at their 1979 meeting, and beginning with this issue the members of USMA will receive *WJM* as a regular benefit of their membership. This will be in the form of a special UTAH EDITION which contains a special section for USMA readers in addition to the usual content of the journal. This special section is prepared by USMA and is under the direction of a Special Editor for Utah. It will provide a forum for communication between the association and its members.

The *WJM* seeks to be a truly useful journal for its readers, the greatest number of whom are practitioners. It seeks to offer a variety of fare which also will include something of interest for students, academicians, researchers and even political leaders of our profession—of whom there are many among its readers. It seeks to reflect the vitality and achievements in science, education and practice that are hallmarks of medicine in the West, and to give these a stronger presence in the medical literature. The editors, the editorial board and many others are dedicated to making this journal a regional instrument of physician education and continuing education in the West, and also an increasingly distinguished journal on the national scene.

The medical profession in Utah has much to contribute as well as to receive from the *WJM*. The University of Utah College of Medicine is of national renown in scholarship, and the state has many innovative leaders in medical practice and health care. It is hoped and expected that some of this scholarship and innovation will find expression in this journal.

We welcome USMA and look forward to a long and productive association which should be of great benefit to all concerned.

—MSMW

Mushroom Poisoning

IT IS SAFE to say that the incidence of mushroom poisoning is directly related to the prevalence of mushroom hunters. For this reason, mushroom toxicity has traditionally been a matter of greater concern in central and eastern Europe than in North America.

Before 1960 very few Americans gathered and ate wild mushrooms, but in the past 20 years there has been a great upsurge of interest in mushrooms in the United States. Thousands of enthusiasts now comb the woods in the summer and fall with field guides, baskets and digging tools. Some of these mushroom hunters are looking for "natural foods" or "natural highs"; others have simply discovered the fascination of a new hobby. While some are cautious and some are bold, a sense of gastronomic adventure pervades this activity, and mushroom poisoning is clearly on the rise.

The incidence of poisoning is difficult to ascertain because reporting is not mandated by law. The US Department of Agriculture Poison Fungus Center received reports of 105 cases with two fatalities in 1973, with only eight states reporting. However, in Colorado alone an average of 50 confirmed cases annually occurred over four years (1972 to 1975). This high incidence was disclosed through the combined efforts of the regional poison center, the Rocky Mountain Mushroom Club and the medical facilities in the state.[1] Therefore, it is likely that the true frequency for the nation as a whole is much higher than the reports suggest.

Approximately 5,000 species of fleshy mushrooms occur in the United States. Generously speaking, no more than 300 of these are likely to attract attention as potential items of food. Of these, approximately 100 species are known to be toxic, at least under some circumstances, and about a dozen are potentially lethal.

At least seven types of mushroom toxicity are known, and there are scattered reports of toxic reactions which fit none of the seven. Most toxicologic studies have been concerned with the most

dangerous varieties. Well over 90 percent of all fatal poisonings throughout the world have been due to a small number of closely related species of the genus *Amanita*. The European "death cap," *Amanita phalloides*, has been responsible for most of the deaths. This mushroom is now known to occur sporadically in the United States, possibly carried accidentally to this continent with the roots of imported ornamental trees.[2] Closely related native mushrooms include the widely distributed "destroying angels" *A virosa, A verna* and *A bisporigera*. All of these mushrooms contain amatoxins, a group of cyclic octapeptides which have been identified as the principal toxins.[3] The amatoxins are thermostable. They are rapidly absorbed from the gastrointestinal tract and cleared by the liver, where they enter hepatocyte nuclei and irreversibly inhibit the enzyme RNA polymerase II, which results in hepatocellular necrosis. In large ingestions the amatoxins also cause renal tubular necrosis by a similar mechanism. A group of inconspicuous brown mushrooms of the genus *Galerina* also contain high concentrations of amatoxins and have occasionally caused fatal poisoning, especially in small children who often seem to be attracted to these little brown mushrooms.

Most of the fatal ingestions not related to the amatoxins have been caused by the false morels of the genera *Gyromitra* and *Helvella*. These contain gyromitrin which, on hydrolysis, releases monomethylhydrazine (MMH). Knowledge of the toxicity of this substance was rapidly advanced by work done at US aerospace centers because monomethylhydrazine has been used extensively as a propellant for rockets.[4] Because MMH is very volatile, cooking may render those mushrooms nontoxic. This fact probably explains the reports, formerly attributed to folklore, that the cook who stirs the *Gyromitra* stew is more likely to become ill than the guests who eat it. The spectrum of toxicity for MMH resembles that of the drug isoniazid. Severe liver damage may occur, occasionally associated with renal failure. Monomethylhydrazine also interferes with the action of pyridoxine, although neurotoxicity is not usually a prominent feature of acute toxicity.

In Europe, severe renal failure has occurred after a latent period of from 5 to as long as 21 days after ingestion of *Cortinarius orellanus* or *Lepiota helveola*. No similar cases have been reported in the United States. However, these mushrooms occur in California, Oregon and Washington, and because of the long latent period the connection between ingestion and illness would be very easy to overlook. The nephrotoxic agents in these mushrooms are unknown.

Among the less life-threatening toxic mushrooms are the "fly agaric" *Amanita muscaria*, and the "panther" *A pantherina*, both of which contain ibotenic acid and muscimol. These indole derivatives induce a syndrome of alternating somnolence and agitation, with visual disturbances and, occasionally, seizures. Although formerly ranked among the serious forms of poisoning, it has become apparent that the illness, while spectacular, is rarely fatal.

Muscarine, once thought to be the major toxic principle in mushroom poisoning, is now known to be present in pharmacologically significant quantities only in a few species in the genera *Clitocybe* and *Inocybe*. The classic triad of salivation, lacrimation and perspiration associated with ingestion of these mushrooms is at present the only indication for administration of atropine, once recommended for all forms of mushroom poisoning.

Psilocybin and its congeners are present in all of the mushrooms which are known to produce true hallucinations. These mushrooms of the genera *Psilocybe, Paneolus, Conocybe* and *Gymnopilus*, are now being sought by some persons as "recreational" mushrooms. Thus far no fatalities have been reported from their use.

Several edible mushrooms are known to interact with ingested ethanol to produce a syndrome similar to that caused by disulfiram with signs of acetaldehydemia. The active substance is a cyclopropanone derivative called coprine, which was simultaneously isolated by two groups of investigators[5,6] from the "inky cap" *Coprinus atramentarius*. Coprine produces prolonged inhibition of acetaldehyde dehydrogenase in vivo. Although several other mushrooms have been reported to produce a similar syndrome, they have not been shown to contain coprine.

Finally, there is a large and heterogeneous group of mushrooms which, with some regularity, cause either upper or lower gastrointestinal irritation, or both. The toxic principles are unknown, and in many cases, differences or similarities in the clinical syndromes are poorly described and documented. The green-spored mushroom *Chlorophyl-*

lum molybdites is one of these. Detailed reporting is needed among these "minor" poisonings, and the report elsewhere in this issue is a welcome addition to the sparse literature in this area.

Among the mysteries surrounding the minor poisonings is the persistent finding that the same species of mushroom may be toxic to some persons and not to others, toxic at some times and not at others, and toxic at some localities and not at others. Until recently much of the available literature has been from European sources. Yet the toxicity of European species seems to differ from that noted in the same, or closely related mushrooms in North America. Two excellent books on mushroom poisoning have become available.[7,8] Both accurately summarize what is known and contain much practical information on diagnosis and treatment.

The mushroom clubs and societies and regional poison centers have been instrumental in providing careful toxinomic identification and in collecting detailed reports of toxic episodes. Especially noteworthy have been the efforts of the Puget Sound Mycological Society and the Rocky Mountain Mushroom Club. Gratifying progress has been made but more needs to be done by both physicians and amateur mycologists to advance the current state of knowledge about these minor poisonings. These episodes while usually not fatal can cause a period of grave discomfort and, not infrequently, require admittance to hospital. It is well to remember also that minor illness becomes major in the very young, the very old and the unwell.

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Medicine by the Decades—Next the 1980's

It is sometimes convenient to divide the course of events into blocks of time such as decades or even centuries. Each of the past four decades has been a special time in the evolution of medicine and health care in this nation, and the 1980's seem likely to be no exception.

In retrospect, during the 1940's World War II produced unprecedented clinical advances in medicine, surgery and psychiatry. With the then readily available funds, both accumulated and new scientific knowledge were applied in often dramatic fashion, and the nation was greatly impressed. The 1950's saw an unprecedented and remarkably productive effort in biomedical research also generously supported by the federal government. The results, both real and speculative, were widely publicized as they developed, and the hopes and expectations of the public for better health began to rise. In the 1960's major legislation was enacted to reap the harvest of this biomedical research and to make its real and imagined benefits more readily available to the public. The goal was to assure access to high quality health care to all. Again it was assumed that all that was needed would be another infusion of dollars. But this time the assumption was somewhat less valid. In the 1970's it began to become apparent that a disparity had come into being between what medical science can do and what the nation, through either the public or private sector, can or is willing to afford. The medical profession and indeed the whole health enterprise found themselves caught in harsh pincers of virtually infinite expectations on the one hand and relatively finite resources on the other. The issue focused on costs and the decade was one of tightening and loosing of the federal pincers, the latter occurring as yet another federal initiative proved ineffective. Thus the stage is set for the 1980's.

It is suggested that the decade of the 1980's will also make its distinctive mark. There are already some signs of what this might be. Modern science and technology are having profound impact not only upon medicine and health care, but upon the nation and world. Besides raising more or less infinite aspirations and expectations in a world of finite resources, modern science and

technology are producing a framework of human as well as technological interdependence which as yet is only poorly recognized, let alone understood. In rough terms aspirations and expectations equate with freedom, independence and personal fulfillment, while a framework of increasing social, economic, political and also technological interdependence equates more with a need for some kind of regulation or control. Both independence and interdependence are central to the very personal issues of health and health care, and it seems reasonable to anticipate that medicine and the health care enterprise will be very much involved in the political as well as the technological process of sorting out new approaches to dealing with these conflicting realities in the 1980's. There are already indications that this may likely be the case.

It would seem that the best and perhaps the only way to maintain freedom and independence within a framework of de facto interdependence is to govern as much as possible by voluntary consensus or agreement among autonomous and independent persons, groups of persons, and institutions within both the public and private sectors. This is quite different from the adversary system which is so much the modus operandi in America today, and which incidentally appears often to create more problems than it is solving. For the 1980's medicine and health care seem to have both problems and opportunities *in spades,* as it were. There is still some freedom and independence for both patients and physicians. The reality of interdependence among all of the components of the system is becoming evident enough. The efforts of government unilaterally to regulate and control the system have not worked and will not work because in our American system the power is too diffuse. It is not all with government and it is not all with the private sector.

It is perhaps worth noting that the issues of independence, interdependence and diffusion of power are surfacing with greater sharpness and in greater complexity in medicine and health care than seems to be happening in other segments of society. It would therefore seem that a real challenge for medicine and the health care enterprise in the 1980's will be to develop an approach to voluntary consensus or agreement among autonomous and independent persons, groups of persons and institutions within both the public and private sectors—and show that it works. A beginning and perhaps exploratory step toward voluntary consensus and agreement may have been taken with the voluntary effort at cost control which is now in its third year. It is significant, and even reassuring to point out that so far the voluntary effort has been comparatively successful, and this may be a hopeful sign for the 1980's.

—MSMW

CASE REPORTS

Refer to: Cheng DS, Williams HJ, Kitahara M: Hereditary hepatosplenomegaly. West J Med 132:70-74, Jan 1980

ABBREVIATIONS USED IN TEXT

LAP = leukocyte alkaline phosphatase
VPRC = volume of packed red cells

Hereditary Hepatosplenomegaly

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HEPATOSPLENOMEGALY is seen in patients with several well-defined underlying disorders. In contrast, primary hepatosplenomegaly is a condition where the underlying cause is not known. A report by Rao and co-workers[1] described seven children in a family with primary splenomegaly and hypersplenism without hepatomegaly. We report a family in whom five of seven siblings had primary hepatosplenomegaly with hematologic evidence of hypersplenism. Subnormal leukocyte alkaline phosphatase (LAP) activity was also found in four of six siblings tested as well as in the mother and maternal grandmother of the propositus, suggesting an autosomal mode of inheritance. There appears to be no relationship between the presence of organomegaly and the LAP activity.

Reports of Cases

CASE 1. The propositus (Figure 1, III-1) is an 18-year-old young man who weighed 6 pounds, 10 ounces at birth, after an uneventful pregnancy, labor and delivery. Soon after birth, he was admitted to hospital for four days because of neonatal jaundice. In the first several years, the patient had numerous upper respiratory tract infections and frequent epistaxis. At the age of 3½ years, splenomegaly was first noted; shortly thereafter, he was admitted to hospital for high fevers and convulsions. The hemoglobin value was 9.8 grams per dl and leukocyte count was 3.6×10^9 per liter, with a differential count of 20 percent neutrophils, 77 percent lymphocytes and 3 percent monocytes. Bone marrow aspiration showed erythroid hyperplasia. A heterophil titer was negative. Tuberculin skin test was negative, and a radiograph of the chest showed no abnormalities. Because of progressive anemia, the patient had to be transfused with a half unit of packed red blood cells.

At the age of 4 years, the patient was referred to the Pediatric Department at the University of Utah Medical Center. Physical examination showed moderate hepatosplenomegaly. A stool specimen was negative for occult blood. Volume of packed red cells (VPRC) was 0.29 liter per liter, with a mean corpuscular volume of 88 femto liters, mean corpuscular hemoglobin concentration of 31 grams per dl and reticulocyte count of 4.4 percent. Blood smear showed abnormal erythrocyte morphology with anisocytosis, poikilocytosis, hypochromia and basophilic stippling. No spherocytes were seen. Coombs test was negative. Osmotic fragility was normal. Serum iron was 48 μg per dl and total iron binding capacity was 410 μg per dl. Serologic test for syphilis was negative. The patient was treated with iron supplements with a rise in his VPRC to 0.33 liter per liter.

He did well with the exception of intermittent epistaxis until 1972, when a second episode of febrile convulsions occurred. Hematologic values were unchanged. In December 1973 recurrent pharyngitis developed in the patient, requiring treatment with antibiotics. Physical examination showed that the liver was palpable 4 cm below the right costal margin with a span of 13 cm. The spleen was palpable 9 cm below the left costal margin. Multiple petechiae were noted on

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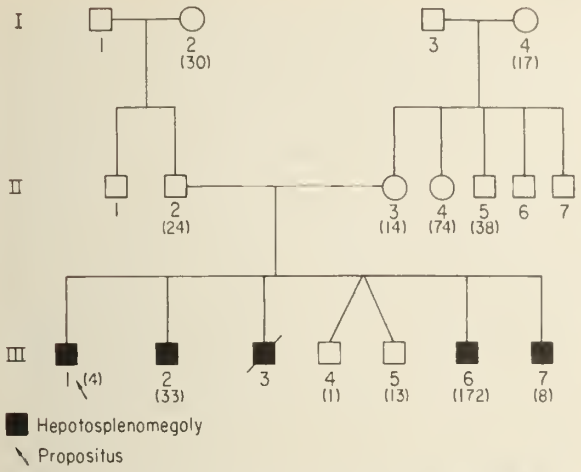

Figure 1.—Pedigree of a family with hereditary hepatosplenomegaly. Numbers in parentheses indicate leukocyte alkaline phosphatase scores.

the lower extremities. The leukocyte count was 1.8×10^9 per liter, with 7.1 percent reticulocytes and a platelet count of 42×10^9 per liter; the blood smear was unremarkable. Screening chemistry panel showed an elevated uric acid of 10.1 mg per dl and an alkaline phosphatase of 152 IU per liter. Hemoglobin electrophoresis was normal. Quantitative immunoglobulin measurements were IgG, 1,700 mg per dl (normal 800 to 1,800); IgA, 120 mg per dl (normal 90 to 450), and IgM, 30 mg per dl (normal 60 to 260). An iliac crest bone marrow aspirate showed substantial erythroid hyperplasia with a myeloid:erythroid ratio of 0.43:1.0. The myeloid maturation was normal. The erythroid series showed megaloblastoid changes. Megakaryocytes were abundant. An iron stain was normal. An iliac crest bone marrow biopsy specimen was hypercellular with an abundance of megakaryocytes. No fibrosis, Gaucher cells or other extraneous cells were seen. Results of a lupus erythematosus (LE) preparation and antinuclear antibody test were negative, and skin tests with streptokinase-streptodornase, mumps, *Candida* and dermatophytes were all nonreactive. Serum folate and vitamin B_{12} levels were within normal limits. Sugar water test for paroxymal nocturnal hemoglobinuria was negative. Glucose-6-phosphate dehydrogenase and pyruvate kinase screens were negative.

Because of pancytopenia presumed secondary to hypersplenism, a splenectomy was done in June 1974. The patient was transfused with platelet packs and did not have any bleeding complications. At laparotomy, the liver appeared

Figure 2.—Normal appearing spleen specimen from case 1 with some reactive changes (reduced from ×400).

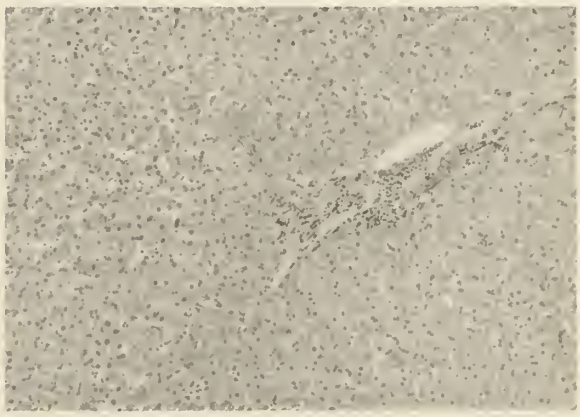

Figure 3.—Liver biopsy specimen from case 1 showing normal parenchyma with a nonspecific portal lymphocyte infiltration (reduced from ×200).

normal. The spleen was large, weighing 1,100 grams. A splenoportogram showed a portal pressure of 27.5 cm of water. The splenic vein pressure was 18 cm of water. Histologic studies of the spleen showed minimal follicular hyperplasia in the white pulp; the red pulp was congested and contained mature lymphocytes (Figure 2). Some areas of fibrosis with iron deposition were also present. There was no evidence of lymphoma or lipid storage diseases. A nonspecific portal lymphocytic infiltration was noted on a wedge liver biopsy specimen (Figure 3). The lymph nodes were normal.

One month following the splenectomy, the patient's leukocyte count was 12.7×10^9 per liter, with a differential count of 50 percent neutrophils, 29 percent lymphocytes, 4 percent monocytes, 12 percent eosinophils and 1 percent basophils. VPRC was 0.43 liter per liter. Reticulocyte count was 1.5 percent and platelet count was 520×10^9 per liter.

Hematologic values have remained normal since then.

In December 1977 the patient was admitted to hospital because of easy bruising, cough, fever, shaking, chills and headache. On physical examination the patient was found to be lethargic, with a temperature of 40.5°C (105°F), absence of nuchal rigidity, injected left tympanic membrane and ecchymoses in the lower extremities. The leukocyte count was 8.2×10^9 per liter. VPRC was 0.44 liter per liter, platelet count was 130×10^9 per liter, and reticulocyte count was 2.2 percent. Analysis of fluid from a spinal tap showed two neutrophils and one mononuclear cell per high-power field, with normal glucose and protein. Numerous Gram-positive cocci in pairs were noted on Gram stain. Subsequent blood and spinal fluid cultures grew *Streptococcus pneumoniae* and the patient was treated appropriately with antibiotics. His hospital course was complicated by disseminated intravascular coagulation, septic shock, acute tubular necrosis requiring hemodialysis, epistaxis, gastrointestinal hemorrhage, mediastinitis and adult respiratory distress syndrome. He recovered fully and was discharged after six weeks in hospital. Blood counts and renal functions have returned to normal. An evaluation of his immunologic status including dinitrochlorobenzene (DNCB) contact sensitivity, opsonization, complements, monocyte function, neutrophil phagocytosis and chemotaxis, and response to pneumococcal polysaccharide immunization were all normal. His leukocyte alkaline phosphatase scores determined by Kaplow's method[2] were 4 and 9 on two different occasions. (Normal values at our laboratory: men 22 to 124, women 33 to 149).[3]

CASE 2 (Figure 1, III-3). A sibling was found to have hepatosplenomegaly, anemia and thrombocytopenia at 1 year of age. At 3 years (1966), his VPRC was 0.18 liter per liter, platelet count was 101×10^9 per liter, reticulocyte count was 11 percent on three occasions, and leukocyte count was 4.6×10^9 per liter with a differential count of 46 percent neutrophils, 44 percent lymphocytes, 9 percent monocytes and 1 percent basophils. Red blood cell fragility and autohemolysis were normal as was a screen for glucose-6-phosphate dehydrogenase deficiency. Bone marrow aspiration showed erythroid hyperplasia. A total bilirubin was 2.4 mg per dl with 1.9 mg indirect bilirubin. Splenic puncture showed no abnormalities and no storage cells were seen. Because of frequent red blood cell transfusion requirements, a splenectomy, liver biopsy and lymph node biopsy were done in November 1966, with identical histologic findings as found in case 1. Eight weeks later, his VPRC was 0.38 liter per liter, leukocyte and platelet counts were 21.8 and 735×10^9 per liter, respectively, and reticulocyte count was 2.0 percent. There had been no transfusion requirement following splenectomy. The patient did well until November 1969, when he died of fulminant pneumococcal septicemia with meningitis, disseminated intravascular coagulation and bilateral adrenocortical hemorrhage. On autopsy there was no evidence of a malignant condition nor was a cause found for the hepatosplenomegaly.

Three other brothers (Figure 1, III-2, III-6 and III-7) also have hepatosplenomegaly although only the youngest brother has abnormal blood counts. He has pancytopenia requiring frequent transfusions. Febrile seizures have also been noted in two of these three involved siblings (Figure 1, III-2 and III-6). Electroencephalographic (EEG) studies showed no abnormalities in any of the siblings except the youngest brother (III-7), in whom there were nonspecific, mildly abnormal findings with excessive 5 to 6 per second theta rhythm over the left hemisphere in drowsiness.

Neither parent (II-2 and II-3) has hepatosplenomegaly and both have normal blood cell counts. The maternal grandparents of the propositus had no organomegaly although anemia associated with chronic congestive heart failure developed in the grandfather. However, with proper therapy, the heart failure resolved and his liver returned to normal size. Splenomegaly, anemia, leukopenia and thrombocytopenia were never present. The paternal grandmother had no organ enlargement. The pedigree is of Swiss, German, Danish, Welsh and Scottish ancestry and there is no family history of consanguinity.

Discussion

Five of seven siblings in the family described had hepatosplenomegaly with hematologic evidence of hypersplenism. Splenectomy was carried out in two of the siblings with normalization of their hematologic values. No secondary causes of hepatosplenomegaly could be found clinically. Splenoportogram studies and appearance of the splenic vein during surgical operation showed no abnormalities in the first case. Microscopic examination of the liver, spleen and lymph node specimens in case 1 and autopsy findings in case

2 also failed to identify the cause of the hepatosplenomegaly. Rao, Shahidi and Opitz[1] described a remarkably similar pedigree. Seven children in their pedigree had a clinically benign form of primary splenomegaly associated with hypersplenism, although hepatomegaly was not seen. Of interest was the presence of seizures in two of their patients. EEG studies showed abnormalities in both of these subjects, as well as in an additional sibling without seizures. A ventricular cyst was found in one of these patients and the suggestion was made that developmental abnormalities of the central nervous system were possibly the result of pleiotropic effects of the "hypersplenism mutation."[1] While four of the seven siblings in our pedigree had seizures associated with fever, none had an epileptiform EEG study. The Rao pedigree were descendants of Dutch immigrants and had no relationship to our pedigree. The authors felt that enlargement of the spleen was most likely due to an autosomal dominant mutation.

Other reports of familial hepatosplenomegaly have been cited in the literature. Holimon and Madge[4] described a family in which four members had hepatosplenomegaly, lymphadenopathy and leukocytosis. Nelson and co-workers[5] described three members of a family in whom a clinically acute but protracted illness with fever, anemia, leukopenia, thrombocytopenia, hepatosplenomegaly, pneumonitis and meningitis developed. The affected subjects all died before the age of 7 years. Extensive infiltration of many organs by lymphocytes, histiocytes and cells resembling lymphoblasts was present. The posterior pituitary glands in two patients were almost completely destroyed by the cellular infiltration.[5] None of these reported familial occurrences of splenomegaly were similar to ours, with the exception of the Rao pedigree—although members of that family did not have hepatomegaly.

Dacie and associates[6] have described *nontropical idiopathic splenomegaly* with evidence of hypersplenism to distinguish this entity from the tropical splenomegaly seen in tropical countries. Dacie's follow-up study of ten subjects showed that malignant lymphomas developed in four of the six patients with long-term follow-up. However, review of histologic studies of the spleen failed to establish criteria for development of malignant lymphoma.[7] Long and Aisenberg[8] reviewed ten cases of idiopathic splenomegaly, none of which developed into lymphoma. Idiopathic splenomegaly was characterized by lymphoreticular hyperplasia with prominent reactive centers in those cases. Careful histologic review of the spleens in our two patients in whom splenectomies had been done did not show any evidence of malignant lesions.

While evaluating the family members, LAP scores were found to be subnormal in four of six siblings studied (Figure 1, III-1, III-4, III-5 and III-7), in the mother (II-3) and in the grandmother (I-4) of the propositus. LAP scores were normal in members I-2, II-2, II-4 and II-5 in the pedigree. This suggests an autosomal inheritance unrelated to the finding of hepatosplenomegaly. Primary LAP deficiency has been reported in a patient with recurrent infections,[9] as well as in a patient with eczema, hyperimmunoglobulin E and repeated infections.[10] Our case had no demonstrable immunologic or neutrophil abnormalities. Familial subnormal LAP activity has been described in three siblings who also had thrombocytopenia and platelet dysfunction abnormalities.[11] In all three cases nonlymphocytic leukemia developed before the patients were ten years old. The clinical importance of a subnormal LAP score in the family in our report is unclear. There were no other disease states present in which LAP activity has been reported to be low.[12] The occurrence of overwhelming pneumococcal sepsis in two of the members is most likely related to their postsplenectomy condition[13] because other members with subnormal LAP scores did not have an increased incidence of infections.

Summary

In five of seven siblings in one family idiopathic hepatosplenomegaly was present, with laboratory evidence of hypersplenism. Splenectomy was done in two patients, with return of hematologic values to normal ranges. Subnormal leukocyte alkaline phosphatase scores were found in four of the siblings but these appeared unrelated to the presence of organomegaly. The subnormal LAP activity appears to be transmitted in an autosomal manner.

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Refer to: Blayney D, Rosenkranz E, Zettner A: Mushroom poisoning from Chlorophyllum molybdites. West J Med 132: 74-77, Jan 1980

Mushroom Poisoning From *Chlorophyllum molybdites*

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THOUGH POISONING from *Chlorophyllum molybdites* is rarely reported, we describe a cluster of three cases of a brief, self-limited gastrointestinal illness associated with ingestion of this fungus. *C molybdites,* previously known as *Lepiota morgani* or the "green parasol" mushroom, occurs in widely scattered geographic areas. In contrast to cases of *Amanita phalloides* or *A muscaria* ingestion, there is almost never a fatal outcome. Our report illustrates two reasons why mushroom poisoning may be occurring with greater frequency: popularity of and confusion with species containing hallucinogens (for example, psilocybin) such as *Psilocybe cubensis* or *P mexicana;* and collection of specimens for consumption by inexperienced persons attempting to eat a "natural" food diet.

Similar symptoms occurred in all our patients. Within one to three hours after eating the fungus, nausea, vomiting, and diarrhea, which was initially watery and then usually became bloody, developed. With supportive therapy, recovery was complete within 24 hours. All three cases occurred within four weeks in the autumn of 1977. In each case the mushrooms were available for identification.

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Reports of Cases

CASE 1. A healthy 46-year-old woman collected several "brown mushrooms" in San Diego's Mission Bay Park. Two hours after eating four of the small, button-like mushrooms in an omelette, she became nauseated and began to sweat, then vomited the meal. She noted several small mushroom fragments in the vomitus. Two dinner companions also consumed the mushrooms, but had no symptoms.

Four hours after dinner, she went to the emergency room of the hospital at the insistence of her friends. She passed three watery stools and vomited clear stomach contents (positive for occult blood). Pupils were 4 mm in diameter and reactive to light. Because of the possibility of *A muscaria* ingestion, she was given atropine sulfate intramuscularly and admitted to hospital for observation. She did not have jaundice, hematemesis, melena, dysuria or previous history of colitis.

On physical examination the patient was anxious, excited, diaphoretic and talked incessantly. Vital signs were blood pressure of 130/70 mm of mercury, pulse 120 per minute, respiration 24 per minute and temperature 35.8° (96.4°F), taken orally. Examination of head, neck, and chest showed no abnormalities. A fourth heart sound was noted on cardiac examination; surgical scars of a previous hysterectomy and left inguinal herniorrhaphy were present. Neurologic examination was normal save for pressure of speech with appropriate content.

Laboratory examination disclosed a leukocyte count of 8,500 per cu mm and a hematocrit of 47 percent. Serum sodium was 141, potassium 3.8, chloride 108 and bicarbonate 25 mEq per liter. Electrocardiogram and radiograph of the chest showed no abnormalities. Examination of two stool specimens failed to disclose any ova or parasites; bacterial cultures did not show enteric pathogens.

On the morning following admission, samples of the mushroom (Figure 1) which accompanied the patient were identified as *C molybdites*. The patient did well and was sent home that afternoon. She returned to the care of her private physician and reported no further symptoms when contacted by telephone a week later.

CASE 2. A 20-year-old woman with chronic

schizophrenia ingested four "small brown spade-like" mushrooms which she found on the lawn of the mental health facility where she had been admitted. Previously, she had used mushrooms found in a different location for their hallucinogenic properties. Two hours after ingestion, nausea, vomiting and diarrhea developed. Five hours after ingestion, the diarrhea became bloody, and she was admitted to hospital for observation. The patient had no history of diarrheal illness at the institution. She had delivered her second child two months previously, and was being given fluphenazine decanoate intramuscularly, trihexyphenidyl, cyproheptadine and ferrous sulfate. She had no previous episodes of hematochezia, melena, hematemesis, colitis, and was not currently using illicit substances.

Physical examination showed a blood pressure of 110/76 and 110/80 mm of mercury without orthostasis, temperature was 36.9°C (98.4°F), orally, and pulse 120 per minute. Examination of head, neck, chest, extremities and heart showed no abnormalities. Multiple abdominal striae were noted. The bowel sounds were hypoactive; the liver and spleen were not enlarged. The neurologic examination showed a withdrawn, moderately obese woman who appeared normal otherwise. Sigmoidoscopy showed pink, nonfriable mucosa without ulcerations or polyps. A Wright-stained smear of the stool showed many bacteria and leukocytes.

Laboratory studies gave the following values: serum sodium was 140, potassium 3.9, chloride 111, and bicarbonate 11 mEq per liter; blood urea nitrogen (BUN) was 12 and creatinine 1.5 mg per dl. Peripheral leukocyte count was 22,200 per cu mm, with 69 percent segmented and 36 percent band forms, 3 percent lymphocytes, 1 percent monocytes and 1 percent basophils. The hemoglobin value was 19.2 grams per dl and hematocrit was 55 percent. An analysis of the urine was remarkable for a specific gravity of 1.024, pH 5.5, protein 3+, numerous leukocytes, moderate bacteria, and numerous coarse granular and fine granular casts per low-power field. Cultures of the urine and blood had no bacterial growth, and two stool specimens were without ova and parasites or growth of enteric pathogens. Radiograph of the chest, barium enema, and electrocardiogram (EKG) showed no abnormalities.

The patient received fluids intravenously and the nausea, vomiting and diarrhea resolved over the next 12 hours. At discharge, 48 hours after admission, abnormalities of the urinary sediment had disappeared, the hematocrit was 43 percent, serum creatinine was 0.6 mg per dl, and no occult blood was found in the stool. Specimens of the mushrooms consumed were identified as *C molybdites* before the patient was discharged from the hospital.

Figure 1.—Various stages of *Chlorophyllum molybdites* ranging from young buttons to fully matured specimens. Only the mature, expanded mushrooms show the characteristic green coloration of gills on the underside of caps due to green spores. Immature spores of younger specimens are white.

CASE 3. A previously healthy 22-year-old man ingested a large, "brown spotted" mushroom found in San Diego's Balboa Park. An hour later he experienced intense nausea and vomiting, yellow colored diarrhea, shaking chills, diaphoresis, salivation, diffuse abdominal pain and diffuse muscle tenderness. He did not have melena, hematochezia or hematemesis. Several hours earlier, the patient had consumed two glasses of red wine and one "Quaalude tablet." He claimed to have previously used similar mushrooms, which he had found in the midwestern United States, for their hallucinogenic effect.

On physicial examination the patient was noted to be shaking and nauseated. Blood pressure was 90/70 mm of mercury supine and 60 systolic in the sitting position. Temperature was 37.7C° (99.9°F) orally, pulse was 100 per minute when the patient was supine and 120, sitting. Head, neck, chest, heart and neurologic examination showed no abnormalities. The abdomen was slightly tender with normoactive bowel sounds and no organomegaly. Occult blood was present in the stool.

Laboratory findings included the following values: hemoglobin 18.6 grams per dl, hematocrit 56.4 percent and 15,000 leukocytes per cu

mm including 28 percent band forms. Serum sodium was 143, potassium 4.2, chloride 105 and bicarbonate 18 mEq per liter. Liver function tests and a radiograph of the chest showed no abnormalities, and an EKG showed only early repolarization. Analysis of the urine showed 3+ proteinuria and 5 to 10 leukocytes, as well as rare leukocyte granular and waxy casts per low-power field. Blood and urine cultures had no bacterial growth.

The patient was treated with fluids given intravenously and supportive care. All symptoms and signs resolved over the next 18 hours. Samples of the responsible mushrooms were identified as *C molybdites*. Analysis of urine and liver function tests gave normal values at the time the patient was discharged, 48 hours after ingestion of the mushrooms.

Discussion

The three patients all had moderately severe, self-limited gastrointestinal illnesses following the ingestion of a common species of mushroom *C molybdites*. While it is possible that these patients had ingested several species of mushrooms, this appears unlikely in view of the following considerations: (1) Only specimens of *C molybdites* were submitted to us by the patients. (2) The areas where the mushrooms were collected by the patients were small and when inspected by us, only *C molybdites* mushrooms were found. (3) These mushrooms grow during a short and limited season and the cases were all confined within a four-week period.

Accounts of *C molybdites* poisonings in the 19th century appear in American and British Commonwealth literature. Perhaps the most illustrative report is giving by McIlvaine and Macadam[1] who quote H. I. Miller of Terre Haute, Indiana:

> Six families here have eaten heartily of them *(C molybdites)*. The experience is that one or two members of each family are made sick, though, in two families, who have several times eaten them no one was made sick. I enjoy them immensely, and never feel the worse for eating them. I doubt if we have a finer flavored fungus.

The authors further quote Professor W. S. Carter of the University of Texas, Galveston, who reported "the poisoning of three laboring men from eating this fungus. They were seriously sick, but recovered." Bessey[2] later mentioned two Michigan residents who consumed green-gilled "shaggy manes" purchased from a local vendor. Vomiting and bloody diarrhea developed in both patients within two hours of eating the cooked mushroom, but both recovered within 24 hours.[2] Cases of *C molybdites* poisoning have resulted in similar gastrointestinal syndromes among immigrant and native Africans.[3,4] The single fatality noted in the literature occurred when a 2-year-old infant died with convulsions 17 hours after eating the raw fungus.[5]

Standard textbooks of mycology generally place *C molybdites* within a nonspecific group of "gastrointestinal toxins." It is widely noted that the fungus appears not to be toxic to all consumers.[1,6-9] A dose-response effect of the poison is inconsistent with the observation that unsusceptible persons may consume large quantities of the fungus without ill effect. Further, because symptoms develop in only a fraction of consumers during an outbreak, geographic variation of the toxin is an inadequate explanation for the variable susceptibility. Because symptoms of perspiration, thirst and giddiness are part of the *C molybdites* poisoning syndrome, it has been suggested that muscarine may play a role in the toxicity.[10] Further speculation has occurred as to the heat stability of the toxin.[4] Many reports, including our first case, are consistent with at least a partially heat-stable toxin. Eilers and Nelson[11] extracted a substance, toxic for mice and chicks, from *C molybdites* found in Florida and concluded that the active principle was a large protein-like molecule, with a molecular weight greater than 400,000 daltons, and consisted of smaller, still toxic subunits of approximately 40,000 to 60,000 daltons. The substance was partially heat labile and subject to proteolytic degradation.

Mature specimens of *C molybdites* are easily recognized by their green spores and gills. No other species among the Amanitaceae bear the spores that lend their green color to the gills on the underside of the cap. The cap measures from 7 to 30 cm, is broad, convex, knobbed or flat. There are numerous scales which are tinged buff to cinnamon in color. The flesh is firm and white. The stalk is 10 to 25 cm long and 10 to 25 mm thick.[1,10] The green spores appear with maturity. Younger specimens (Figure 1) have white gills or are button shaped, and may be confused with the edible *Leucoagaricus rachodes* and *L procerus*.[6] A method of identification of the green spores of *C molybdites* in vomitus and stool specimens has been described, using filtration and microscopic examination for the presence of basidiospores of the fungus.[12] In the absence of the

whole mushroom, this can be a useful method to confirm mushroom ingestion.

C molybdites is common in the warmer midwestern United States, but rarely found in New England. It is seen from New Jersey to Iowa, southwest through Arizona and Texas,[13] and in southern California.[14] The species seems to thrive in warmer climates and occurs in the Philippines, Tahiti, the West Indies, Brazil, Rhodesia[4] and Kenya.[3] Colonies of the fungus are noted to assume a "fairy ring" configuration and are characteristically found in meadows, short grasslands, lawns, and parks after spring and autumn rains.

The green-spored mushrooms *C molybdites* (also known as *Lepiota morgani*) contain a poison which affects some persons yet is harmless to others. In susceptible persons, ingestion of either raw or cooked mushrooms is followed by nausea, vomiting and diarrhea within one to six hours. The diarrhea may turn bloody, and may contain leukocytes. Diaphoresis, tachycardia and postural hypotension may also be seen. Predominance of parasympathomimetic symptoms—pupillary constriction, salivation and lacrimation—are not features of the syndrome and may help to distinguish these cases from those involving *Amanita muscaria*. There is minimal or no fever, and objective abdominal findings are minimal. Leukocytosis may be seen; there may be transitory abnormalities of the urinary sediment including microscopic hematuria, proteinuria and cylinduria. Supportive care, including maintenance of fluid and electrolyte balance should result in complete recovery within 24 to 48 hours. As in all poisonings, it is useful to have specimens of the offending agent available for identification. Observation for a longer period is warranted if *A phalloides* poisoning cannot be ruled out because of the well-known delay in the appearance of toxic manifestations after ingestion of this mushroom.[15,16]

There is renewed interest in gathering mushrooms by inexperienced collectors for both pharmacologic and nutritional use. Physicians may be called to evaluate and treat inadvertent consumption of *C molybdites* as well as more toxic species with increasing frequency.

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Refer to: Marini JJ, Bilnoski W, Huseby JS: Acute cor pulmonale resulting from tumor microembolism. West J Med 132: 77-80, Jan 1980

Acute Cor Pulmonale Resulting From Tumor Microembolism

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ALTHOUGH lung parenchymal metastatic lesions are relatively common, selective compromise of the pulmonary vasculature due to tumor embolism is rare. This report concerns a case of acute cor pulmonale that developed as a manifestation of diffuse microembolism from previously quiescent metastatic carcinoma.

Report of a Case

A 49-year-old woman was admitted to hospital with a complaint of increasingly severe dyspnea of three days' duration. Five years earlier, surgical excision of a compressive epidural mass established the diagnosis of metastatic adenocarcinoma but resulted in paraplegia at the T-2 level. Subsequently, a primary malignant tumor of the breast was discovered, and left simple mastectomy and oophorectomy were done. In the absence of

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other clinically apparent metastatic lesions, hormones, radiation and chemotherapy were not administered.

Except for intermittent minor back pain, the course before the sudden deterioration in the patient's condition was uneventful. Specifically, there were no indications of cardiovascular or pulmonary disease. No evidence of metastasis or respiratory compromise was noted on a routine clinic visit 12 days before the patient's death, and there were no symptoms until three days before admission. At that time dyspnea developed gradually and intensified rapidly, without accompanying chest pain, hemoptysis, fever or sputum production.

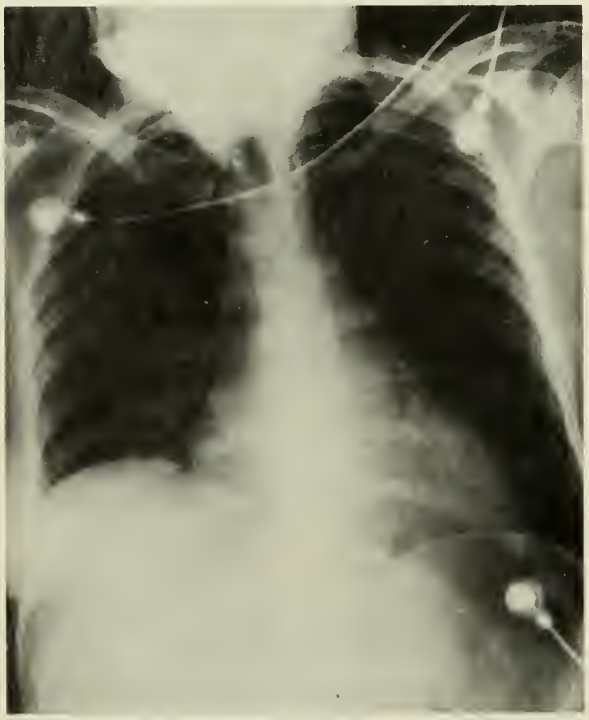

Figure 1.—Supine anteroposterior roentgenogram of the chest on the day of admission.

Figure 2.—Anteroposterior perfusion lung scan showing multiple bilateral subsegmental defects.

At presentation the patient appeared well-nourished, cyanotic, mildly lethargic and in severe respiratory distress. The blood pressure was 60/50 mm of mercury, the pulse rate was 88 per minute, the respirations were 66 per minute and the temperature taken orally was 36°C (96.8°F). The skin, head, eyes, ears, nose and throat appeared normal. The pulmonary examination showed scattered basilar rales and symmetrical breath sounds without wheezes or rubs. The precordium was hyperdynamic with a left sternal lift. The heart sounds were normal. No murmurs or gallops were heard on auscultation, and no soft tissue edema was evident. The remainder of the physical examination findings were within normal limits.

Arterial blood gas determinations, carried out while the patient was breathing room air, showed the following: pH, 7.36; oxygen tension (Po_2), 47 torr, and carbon dioxide tension (Pco_2), 19 torr. Serum electrolyte values were sodium, 141; chloride, 99; potassium, 6.0, and bicarbonate, 8 mEq per liter. The blood urea nitrogen was 47 mg per dl; glucose, 199 mg per dl; hematocrit, 31 percent and leukocyte count, 21,200 per cu mm, with polymorphonuclear predominance. The erythrocyte sedimentation rate (Westergren) was 87 mm per hour.

A radiologist judged a roentgenogram of the chest to be normal (Figure 1). An electrocardiogram showed deep symmetrical T-wave inversions in leads V_1-V_3, without evidence of specific chamber hypertrophy. A perfusion lung scan with macroaggregated albumin labeled with technetium 99 showed multiple small peripheral defects (Figure 2) which were interpreted to be uncharacteristic of pulmonary emboli. With the patient receiving 40 percent oxygen by mask, emergency catheterization of the right ventricle was done and produced the following data: mean right atrial pressure, 15; right ventricular pressure, 50/15; pulmonary artery pressure, 50/25, and wedge pressure, 10 mm of mercury. Hypotension and tachypnea continued despite administration of fluids intravenously, antibiotics and oxygen. The patient died six hours following admission.

At autopsy major involvement of bone and lung vasculature with adenocarcinoma was found. The vertebral column was extensively replaced by neoplastic tissue. The weights of the right and

left lungs were normal at 450 grams and 350 grams, respectively.[1] The pathologist estimated that microscopic tumor emboli obstructed 60 percent to 75 percent of pulmonary arterioles, without occluding vessels larger than 0.4 mm in diameter (Figure 3). All macroscopic pulmonary arterial vessels were widely patent and grossly of normal caliber and thickness. No macroscopic thrombi or bland emboli were found. Various stages of endovascular organization were represented in all sections of lung examined microscopically. Numerous areas of hemorrhagic pulmonary infarction estimated to be 48 to 72 hours old were present in the lung periphery. Lung parenchymal invasion by tumor was not detected.

A solitary tumor nodule (0.9 mm in diameter) was found in the right lobe of the liver. Microscopic carcinoma was also recovered from pericardial fat and adrenal tissue but was not macroscopically apparent. No other sites of carcinoma were found. No evidence of cardiac chamber hypertrophy, coronary artery occlusion, valve abnormality or myocardial damage was detected. Specifically, the heart weight was within normal limits at 240 grams and the right ventricular free wall thickness was at the upper limit of the normal range at 5 mm.[2]

Discussion

Despite the unexpectedly high frequency of microscopic tumor deposits within pulmonary vessels demonstrable at autopsy,[3,4] pulmonary hypertension resulting from tumor embolism is both uncommon and rarely suspected during life.

Pulmonary vascular compromise by carcinoma may result from embolization of central or microscopic vessels or from lymphatic encroachment on small vessels.[5] Although several well-documented cases of acute right ventricular failure due to massive tumor occlusion of central pulmonary arteries have been reported,[3,6] acute respiratory distress in previously asymptomatic patients associated with tumor microembolism has been described in only a single report of two cases,[7] and in neither instance was hemodynamic impairment confirmed premortem.

Characteristically, symptoms resulting from pulmonary microemboli advance slowly. In 1937 Brill and Robertson[8] described four patients in whom dyspnea resulting from obliteration of small vessels by tumor progressed to a fatal outcome over a several week period, and suggested the term *subacute cor pulmonale*. Since that initial

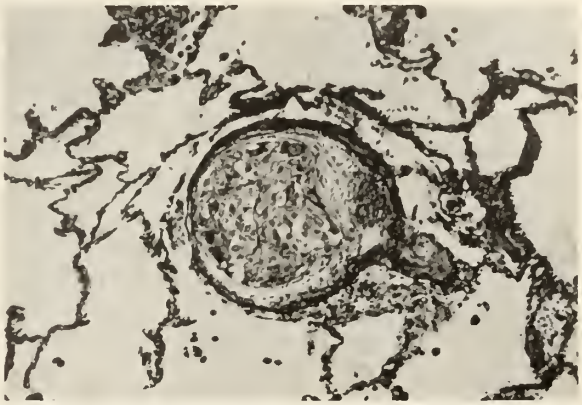

Figure 3.—Photomicrograph of a pulmonary microvessel occluded by adenocarcinoma. Note that no invasion of the elastic laminae is evident. (Verhoeff—van Gieson stain, enlarged 1.4× from original magnification ×450).

report fewer than 30 cases of respiratory compromise associated with tumor microembolism alone (without parenchymal, lymphangitic or central artery involvement) have been described in the English language literature.[3-5,7-14] In all but the two cases cited above, the clinical course from onset of symptoms to death has varied from ten days to several months, and an insidious course has been emphasized.

Because our patient presented with symptoms and findings of acute right ventricular failure, massive venous thromboembolism was suspected. The acuteness of decompensation is supported by the three-day course from first symptoms to death, and the normal right ventricular wall thickness found at autopsy. In addition, the association of a high right ventricular filling pressure with a modest elevation of mean pulmonary artery pressure is suggestive of an acute course; Sasahara[15] has shown that most patients who have massive venous thromboembolism and a nonhypertrophied right ventricle cannot sustain mean pulmonary artery pressures of 30 mm of mercury or greater without decompensation.

Pulmonary tumor emboli most frequently originate from neoplasms of trophoblastic, breast, hepatic and gastric tissues,[3-5,7,9] and appear to differ from true metastatic lesions because the aggregates of tumor cells remain within vessels, rarely invade lung parenchyma,[16,17] and are eventually destroyed by a process of endovascular thrombosis and organization. If further embolization can be halted, therefore, diffuse pulmonary vascular involvement by tumor does not necessarily signify a terminal stage of illness.

Recognition of diffuse tumor microembolism is

difficult, but has important implications for management. Both lung scan and angiographic features are nonspecific, and a lung biopsy is required to establish the diagnosis firmly. In patients with treatable neoplasms who present with acute cor pulmonale, diffuse tumor microembolism should be considered, however, because appropriate management includes withholding anticoagulants and correction of hypoxia and acidosis to reduce pulmonary hypertension until treatment of the underlying neoplasm is effective.

Summary

Within 72 hours a rapidly progressive dyspnea and right ventricular failure developed in a previously asymptomatic woman with adenocarcinoma. At autopsy, extensive tumor occlusion of the pulmonary microvasculature was found without macroscopic vessel involvement. In susceptible patients, tumor microembolism is a potentially treatable cause of acute cor pulmonale and may closely mimic massive thrombotic embolism.

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Orthodox Medicine Humanistic Medicine Holistic Health Care

BEGINNING IN THE December 1979 issue the editors of THE WESTERN JOURNAL OF MEDICINE began a forum for dialogue and discussion of orthodox medicine, humanistic medicine and holistic health care. The forum was initiated with statements by persons known to have an interest in and knowledge of this subject. Readers are invited to submit their views constructively and succinctly. As many as space permits will be published in future issues of the journal. At an appropriate time all of the material, published and unpublished, will be collated and, if possible, a distillate will be prepared to summarize the dialogue and discussion.

—MSMW

Care of the Patient

LOUIS K. DIAMOND, MD

WITH REGARD to the articles and the editorial on "Orthodox Medicine, Humanistic Medicine and Holistic Health Care" in the December issue, I would like to call attention to talks given at Harvard Medical School when I was a student many years ago.[1-3] They were by the famous Francis W. Peabody, physician-in-chief at the Boston City Hospital, on the subject of "The Care of the Patient." He emphasized the importance of what is now called by the fancy names "humanistic medicine and holistic health care." Dr. Peabody stated that "scientific medicine" could not replace the care of the patient, and that there had to be a blending of all approaches to make the patient comfortable and contented with his life as well as to help overcome his disease. Everything Dr. Peabody told us then applies equally well to our present problems.

I would strongly reject dividing medicine into scientific, humanistic and holistic. Of course it should be scientific up to the limits of our scientific knowledge. The term humanistic medicine may be more appropriately used to distinguish it from veterinary medicine. As for holistic, this is what we used to call "total medical care" which includes physical, mental, emotional, and the many other subdivisions which have unfortunately been permitted to develop under the self-serving stimulus of nature-healers, food-faddists, bone-manipulators, gurus, and other such "specialists."

The old-fashioned family doctor tried to treat the whole person, not just isolated parts of him, and did not give this up as medical science advanced. Of course, he had to call in skilled specialists on occasion, but even then he remained available to support his patient and the family as necessary. The mistake made lately, particularly in teaching young physicians, is to think that science can totally replace, instead of being incorporated in, what is being called holistic health care. It is still just the care of the patient, using the knowledge and wisdom accumulated through the ages. This should be the physician's guiding principle in the practice of medicine. And we should teach as well as constantly remember the value of what we listed as number 1 in the Order Book for every new admission, "give t.l.c., q.s., p.r.n." Only so may we retain or regain the respect and affection of our patients.

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Compassion and Competence

E. R. W. FOX, MD

"EVERY PATIENT carries his own doctor around inside him. The physician in attendance must help the patient use that 'inner doctor' to hasten his recovery. Each individual should be looked upon as a whole person, not as a disease entity." These words were spoken not by a physician but by a

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layman: Norman Cousins, who until recently was editor and publisher of the *Saturday Review,* as he addressed the opening session of the annual meeting of the American College of Surgeons.

Cousins, as a new champion of holistic medicine, leveled sharp criticism at some members of the medical profession, aiming his barbs at our callous, or at least thoughtless, handling of patients as they recover from surgical operations or from illness. Basing his observations on his own experiences with a degenerative collagen disease, he urged a return to the simpler, more personal type of medical care in which patient and physician are collaborators, rather than adversaries, in their search for a return to health.

Even the most casual observer must be aware that Cousins and other proponents of holistic medicine are now being taken seriously by physicians and academicians alike. Cousins has been installed as the Senior Lecturer on Medical Humanities at the UCLA School of Medicine. Other medical schools are once again adopting curricula that include the humanities. Scientific publications, including the prestigious *JAMA* and the *New England Journal of Medicine,* are carrying more "nonscientific" articles on holistic medicine. Cousins has just published a book, *The Anatomy of an Illness,* that promises to be a best seller.

It is significant that even though there was the usual display of the newest and most exotic technologies at last October's meeting of the American College of Surgeons there were, in addition, an increasing number of presentations devoted to the human side of surgical therapy. We heard, for example, a fine lecture entitled "Compassion and Competence: The Prerequisites of a Surgeon."

The basic concept of holistic medicine is, of course, that we physicians should be making better use of the body's natural resources in the restoration of health, relying less on sophisticated technology. We are overtesting and overtreating. We stand accused of having forgotten that "we make our own cortisone."

A somewhat gentler criticism of the modern medicine man is that we take ourselves and our sophisticated therapeutics a bit too seriously. We fail to use the healing qualities of humor. Research workers at Stanford Medical School have shown that there are physiological reasons why "humor is beautiful medicine." Laughter actually lowers sedimentation rates. Laughter produces endorphins that relieve pain. Laughter shortens hospital stays. Doctors, by using humor, can program a patient to live.

All this is not exactly a new concept for the *old fashioned* physician who practiced in the prepenicillin days. This doctor—whose logo was the little black bag, who was so often unable to offer much more than concern and kindness—was well aware that happiness heals. Yet, this same physician who has watched with wonder the evolution of modern medical care hopes that we do not turn back the clock in our pursuit of *naturalness,* whether it be health foods, home birthing or the nihilism that some proponents of holistic health care espouse. Rather, each day as we send up thanks for the miracles of modern technology let us also thank humanists such as Cousins for reminding us that there are alternatives in health care and that competence *and* compassion are prerequisites, not for surgeons alone, but for all practicing physicians.

A Pluralistic Approach

JOHN R. GREEN, MD

THOUGHTFUL REVIEW of the manuscripts of Malcolm C. Todd ("Interface: Holistic Health and Traditional Medicine"), Rick J. Carlson ("Holism and Reductionism . . ."), James Vargiu and Naomi Remen ("What Is Health For? . . ."), Marc Lappé ("Holistic Health: . . ."), Richard H. Svihus ("On Healing the Whole Person: A Perspective"), Kenneth R. Pelletier ("Holistic Medicine: From Pathology to Prevention"), and John P. Bunker and William G. Gerber ("Holistic Health Care . . .") indicates a reaffirmation of the Hippocratic and Oslerian principles of medicine.

Medical history is replete with examples of varying degrees of orthodoxy, science, sectarianism, humanism, generosity and selfishness in rapidly changing societies. Medical ethics have developed as a code of behavior for physicians with the purpose of benefiting patients. Because physicians differ in cultural backgrounds, training, available energy and interests, it is understandable that some will emphasize certain aspects

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of medicine more than others. A pluralistic approach is healthy and necessary, including the recognition as to when to utilize consulting and ancillary services for preventive and therapeutic measures. However, all of medicine is one and physicians should play the leading role in its application.

Personal Investment in Health

THOMAS L. PETTY, MD

THE CURRENT REPOPULARIZATION of wholistic (or holistic) medicine appeals to me from several points of view. First, its historical roots, dating to the advice of Hippocrates and much later but at the beginnings of modern internal medicine in this country from Sir William Osler, clearly indicate that this is not some new thought or a cult engendered by contemporary society. Second, even though I have been thrilled by technological advances in medicine, and particularly in my field, which includes intensive respiratory care, none of this is really very important if the intact human being cannot resume normal life's activities. In fact, were the precepts of wholistic medicine well established, a good portion of intensive care would become unnecessary. Third, as both a scientist and primary care giver I frankly see no competition between the basic tenets of wholistic medicine and modern medical technology.

It is apparent to me that many of the problems within the pulmonary field are related to behavior and life-style. A cessation or major reduction in the consumption of tobacco products would be the most important step in reducing the impact of emphysema, chronic bronchitis, lung cancer and even so-called occupational lung diseases, to say nothing of other smoking-related diseases, such as coronary artery disease and urinary tract carcinoma. Thus the objectives of maintenance of health and prevention of disease could be readily translated into reduced impact of disease and socioeconomic burden for our country were we to choose a more healthy life-style.

Even for patients with advanced disease we have always believed and taught that "the patient should be a member of his or her own health care team." This is particularly true in any chronic disease where understanding of disease process and participation in care are crucial to a successful outcome.

It was said sometime ago that the best approach to a long happy life was to acquire a chronic disease and take good care of it (paraphrasing). Even better would be a new health approach designed to promote happy, healthful living through personal investment in one's self. Thus from every point of view, including research, teaching and patient care, I heartily embrace the populist movement toward humanism in medicine which may well be met through wholistic medical care. However, there is really nothing new about wholism in medicine.

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The Challenge of the Next Decade

JOE P. TUPIN, MD

I FOUND THE PRESENTATIONS in the forum in the December issue stimulating but unfortunately diverse. Perhaps on further reflection this is not so unfortunate because it seems to me that at least one thrust of these articles is to suggest that *orthodox medicine* has become narrow, inflexible and resistant to new perspectives. Consequently, the definitions, opinions and descriptions of the scope of holistic and humanistic programs should be, perhaps must be, broad, variable and subject to perspective.

However, embedded in this idea is the suggestion that these new approaches stand in creative tension with orthodox or allopathic medicine. Words, also, such as *opposition* and *competition* are used in this same comparison. I find this singularly distracting and unfortunate. I am firmly convinced that orthodox medicine has brought a great deal of insight to both illness and health,

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and to suggest that one of these new approaches may supersede what has served us well seems unfortunate in the extreme. Rather, I believe one can hear in this debate the hope that orthodox medicine can expand its concepts and perspective. This hope embodies the fervent belief that the mind, body and soul are one and that the health practitioner or physician must acknowledge and respond to each level. The argument is further advanced that health is a personal responsibility and that each individual, potential patient, has the right to choose from among a variety of alternatives of health care and treatment for disease. Should all such options be of equal desirability then such an egalitarian approach might be justified. Nonetheless, I think embedded even in the most open description of these new forms there is an implication that there are some avenues that lie outside even their boundaries. Thus, if boundaries must be drawn the issue seems to be careful consideration of the criterion of that boundary contruction, identifying goals that the criterion will serve and determining who is qualified to apply such a criterion. Once this set of ground rules is agreed upon, then they let us back again on familiar territory.

This brings me to the second concern that I have about some arguments for the most open approach to health care, and that is the arguments are fundamentally antiscientific. Science does not automatically, routinely or necessarily require antihumanistic or organ orientation, rather principles of scientific investigation and proof can be applied, and indeed routinely are, to the *soft sciences*. Scientists make science, apply its principles just as physicians apply the principles of orthodox medicine, thus condemnation of broad, theoretical, philosophical perspectives seems not to be the issue, but rather the selection, training and supervision of individual practitioners will more likely insure the achievement of the goals outlined in this forum. None can quarrel with the need to expand, review and continuously update our knowledge nor to carefully review our attitude toward patients and their families. Indeed there is a seduction in the logic and organization of orthodox medicine and the excitement of its discovery which lead practitioners away from the cultural, social and psychological aspects of patients. The consequence is not to substitute holistic perspectives for orthodox medicine, but rather to integrate. This I think is the challenge of the next decade.

A Balance of Science and Art

DWIGHT L. WILBUR, MD

WILLIAM ALLEN WHITE, the great Kansas editor, many years ago cogently wrote that "life is largely subjective." In other words, it is largely what we believe and think it is. There is no greater application of this thought than in the broad field of health and it may refer to families, communities or other groups of people, as well as individual persons. It accounts in large part for the important place in history and even in present-day life of the medicine man, the magician, and the healing power of prayer and religion. It encompasses much of what we call the art of medicine and of the stated principles of many forms of healing arts. It is an important factor in the placebo response, that fascinating reaction to inert substances which is noted in some 35 percent of Americans. It accounts in part for the great variability in the emotional, physical and psychological responses of individual persons and groups in the same setting to a situation and even to a disease. There is really nothing new about these subjective responses except for the carefully carried out scientific studies in recent years of the physiologic responses to psychic and emotional stimuli and to the placebo response.

As I read about *humanistic medicine* and *holistic health care,* I find nothing that is really new except perhaps broader use of the terms and the greater and broader interest in them by many people who purport to use them in attaining better health and thereby attempt to avoid and treat disease. I find no new principles, no scientific evidence outside of what is surely an important part of so-called *orthodox medicine*. The latter has always encompassed the whole person—the psyche as well as the soma and the interrelationships of physical, emotional and psychic factors in health and disease.

What then is the difference, if any? There is really none but there has been, I believe, a shift in balance or emphasis. On the one hand there have been great advances in the broad field of

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scientific medicine in this century and, on the other hand, because of this avalanche in science, a somewhat lessened emphasis on the psyche and the impact of emotions on health and disease. If there has been imbalance, it has been quantitative and not qualitative. Another significant factor has been the great difficulty in obtaining sound scientific data on these latter, less tangible aspects of health and disease. The advances in scientific information about health and the prevention and treatment of disease accompanied by amazing technological progress have come so rapidly and been so great in number that they have far outstretched the ability of the medical profession generally, and people in particular, to keep up with them. In a natural environment in which more people receive general education, there are fewer illiterates and more freedom in terms of time and improved economic conditions, there has been a welling up of interest in health and medicine. This widespread concern and involvement by many persons outside of the medical profession has accounted for the growing interest in alternative methods of health care. In the balance between scientific advances in medicine and the individual person, the scales for some years have been weighed more heavily in the direction of medical science.

The great needs today in the field of health and medicine are the following:

- To continue scientific advances in the basic medical sciences and indeed in all aspects of medicine and health.
- To reestablish a proper balance of the science and the art of medicine in keeping with the long tradition of medicine.
- To encourage education of all people, and particularly children, as to their own personal health and their personal *responsibilities* to attain and maintain it through proper nutrition; the development of a healthy attitude toward themselves and life; proper exercise, rest and relaxation; avoiding harmful agents as much as possible, and establishing periods of freedom from tension.
- To make available to everyone at reasonable cost and with easy access, medical and health care of high quality.

It seems to me the prime role of those with interest in humanistic medicine and holistic health care relates to the third factor noted above, namely the factor of education regarding health. Perhaps as time progresses methods of investigation and research can be developed that will put what the disciples and practitioners of these arts believe in on a more sound and rational basis and less on a subjective and anecdotal one.

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Orthodox, Humanistic and Holistic

To the Editor: Publishing a forum on "Orthodox Medicine, Humanistic Medicine and Holistic Health Care" is appropriate, timely and much needed. While I am neither an expert nor an enthusiast on the concepts of holistic health care, I do have interest and concern. Interest because there is much mysticism and absence of fact with considerable empiric observation suggesting value. Concern because the field is wide open to abuse, entrepreneurism, quackery and charlatanism.

The papers in the December issue are well done. They are a fine first step in definition and description of the problem. They also hold the possibility of stimulating further work, verification of issues and a guide to policy making. I commend and encourage you.

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Mannitol in Dysbarism

To the Editor: I read with interest the review of mannitol by Nissenson and co-workers in the October issue. Although the usefulness of mannitol in treating a number of cerebrovascular and other diseases was enumerated in the article, at least one specific use of this agent was not mentioned which deserves comment. This is the use of mannitol in treating type II decompression sickness and air embolism.

In Hawaii, where more cases of dysbarism are treated than in any other location in the world, mannitol is not infrequently used as an adjunctive drug in the treatment of severe decompression sickness and air embolism. A large number of these types of cases also are treated in southern California, as well as some cases occurring elsewhere along the Pacific Coast. The treatment experience using mannitol in these areas is not known. One case from England has been reported in which mannitol was used along with other drugs to treat neurological decompression sickness without recompression.[1]

The pathogenesis of type II decompression sickness is much more complex than the simple occurrence of intravascular gas bubbles. Other important pathophysiological phenomena associated with severe decompression sickness include denaturation of plasma proteins, hyperlipoproteinemia, pulmonary and systemic fat embolization, platelet aggregation and thrombocytopenia, activation of the clotting system and red cell clumping. These various blood-bubble interactions combine to produce microvascular stasis, thrombosis, vascular endothelial damage from ischemia and plasma loss—all of which can produce significant "third-spacing" hemoconcentration and, sometimes, vascular collapse.

In dysbaric tissues having impaired microvascular perfusion, the restoration of minimally adequate circulation is often not accomplished by recompression alone. The presence of blood aggregate thrombi and vascular endothelial cell damage result in progressive ischemic tissue damage despite clearing the gas bubbles from the circulation. Mannitol is useful in treating these cases because it increases extracellular fluid osmolality, which acts to reduce cerebral edema and restores microvascular perfusion, as was discussed in the October article by Nissenson.

All physicians called upon to treat cases of dysbarism should be familiar with the use of mannitol because it can be a very helpful drug in managing these types of patients.

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Refer to: Petrakis NL: Diagonal earlobe creases, type A behavior and the death of Emperor Hadrian (Medicine in Perspective). West J Med 132:87-91, Jan 1980

Diagonal Earlobe Creases, Type A Behavior and the Death of Emperor Hadrian

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Classical writings suggest that the Roman emperor Hadrian died from congestive heart failure resulting from hypertension and coronary atherosclerosis. This diagnosis is supported by the identification of bilateral diagonal ear creases on sculptures of several busts of Hadrian as well as literary evidence of behavior pattern A.

THE FEW DETAILS known of the illnesses and causes of death of ancient historical persons come from the writings of classical historians such as Gaius Suetonius Tranquillis,[1] Dio Cassius[2] and the compilers of the *Scriptores Historia Augustae,*[3] and from works of modern paleopathologists.[4] In 1911 Kanngiesser[5] reviewed the descriptions of the deaths of the Macedonian Alexander the Great and the Roman emperors Claudius, Trajan and Hadrian. In making diagnostic inferences about the illnesses leading to their deaths, Kanngiesser recognized that sources of historical information unknown to him or the development of newer diagnostic methods might lead to different conclusions in the future. This paper attempts to apply a recently described physical sign and newer knowledge on personality and disease to the illness of the Roman emperor Hadrian (76 to 138 AD).*

*Dr. Otto E. Guttentag provided clinical suggestions and assisted in German translation. Susan L. Petrakis located ancient references to Hadrian.

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Dio Cassius, writing about 80 years after Hadrian's death, provided the primary source of the details of Hadrian's illness. The *Historia Augustae,* written about 260 years later provides some further information on the emperor's illness. The material in the *Historia Augustae* appears to have been drawn from Dio Cassius and possibly from an autobiography of Hadrian no longer extant.

According to Dio Cassius, Emperor Hadrian became ill in the year 136 AD, when he was 60 years old. The nosebleeds, from which he had long suffered, intensified, and he began to despair of his life. "Hadrian did linger on a long time in his illness, and often prayed that he might expire and often desired to kill himself." In 138 AD, the next date for which any details of illness are given, Hadrian's clinical condition had worsened. "Hadrian became consumptive† as a result of his great loss of blood, and this led to dropsy." With

†The interpretation of consumptive refers to body wasting from prolonged illness, not tuberculosis. The key word in this translation is φθόη which can be interpreted to mean faded, loss of weight or wasting away. An earlier translation of Dio Cassius by Manning[6] was "(H)Adrian lost so great a quantity of blood he became a skeleton, and afterwards dropsical."

treatment by "certain charms and magic rites he would be relieved of dropsy for a time but would refill with water."

Since, therefore, he was constantly growing worse and might be said to be dying day by day, he began to long for death; often he would ask for poison or a sword, but no one would give them to him. . . . Finally he abandoned his careful regimen and by indulging in unsuitable foods and drinks met his death, shouting aloud the popular saying, "Many physicians have slain a king."

The history of recurrent epistaxis and edema suggests the possibility of an underlying hypertension which progressed to congestive heart failure. There is no record of dyspnea, cough or angina pectoris. Possibly, anemia from the nosebleeds may have been the precipitating factor. An alternative cause of recurrent epistaxis is a rare genetically dominant trait, hereditary telangiectasia, which may lead to severe anemia. However, the absence of any recording of it in Hadrian's family by the historians makes it unlikely. Although the edema could represent the nephrotic phase of latent glomerulonephritis, this diagnosis is much less common in patients of Hadrian's age. Numerous other diagnoses could be considered such as valvular disease, cirrhosis or malnutrition. But Hadrian's superb physical health during all but the last two years of his life makes most of these less likely. Kanngiesser[5] diagnosed Hadrian's death as due to "vitium cordis and chronic nephritis." In the medical era of 1911, an elderly patient with severe edema, in the absence of other signs, would be likely to receive a diagnosis of chronic nephritis. The term "vitium" (Latin: *vitiare*—faulty or defective) is nonspecific, probably denoting a cardiac condition considered to be a secondary effect of renal failure.

Elevation of blood pressure is the most common cause of congestive heart failure among middle-aged and elderly patients.[7,8] It is known that most hypertensive persons who are left untreated eventually develop left ventricular hypertrophy leading to cardiac enlargement and, after many years, to death from clinical coronary disease, congestive heart failure or a combination of both. In recent studies, coronary atherosclerosis has been found in over 90 percent of patients dying with hypertension.[8] The predominant importance of coronary atherosclerosis in determining the manifestations of hypertensive heart disease has been emphasized by Friedberg.[9] From this evidence I have hypothesized that Hadrian probably died from hypertensive and coronary arteriosclerotic disease. Although the absence of information on a history of chest pain or pulmonary symptoms is troublesome with respect to this diagnosis, it is now recognized that a great many persons have silent coronary disease that progresses directly to congestive heart failure without exhibiting the classical clinical symptoms.[7,10,11] Two characteristics reported to be associated with coronary atherosclerosis have been found in Hadrian's case: (1) bilateral diagonal ear creases on busts of Hadrian and (2) literary evidence suggesting that the emperor exhibited a type A behavior pattern.

The association between ear creases and coronary artery disease was first noticed in the mid 1960's, and Frank in 1973[12] appears to be the first to report that a bilateral or unilateral prominent ear crease in the lobule of the earlobe was present in a large proportion of his patients who had one or more risk factors for coronary heart disease. Since Frank's description, several reports have been published describing the association of the diagonal ear crease with coronary atherosclerotic heart disease.[13-19]

It should be noted that Rhoads and colleagues[20] found a very low predictive value for the ear crease in a Japanese-American community that had a low prevalence of clinical coronary heart disease. The relationship between the predictive value of clinical and laboratory tests and the prevalence of the specific disease has been discussed by Galen and Gambino.[21] The frequency of diagonal ear creases in the apparently healthy general population increases with age beginning after age 30. The sign has little prognostic value for screening the general population where the prevalence of clinical coronary disease is low,[20,22] but appears to support the diagnosis in patients in hospital with other clinical signs suggesting coronary artery disease, particularly in patients between the ages of 50 and 70 years. Investigators have observed the presence of diagonal ear creases in a high proportion of patients with a clinical diagnosis of coronary heart disease as compared with patients with other diseases.[13,17-19] The significance of this sign has been investigated in patients undergoing coronary artery catheterization as well. Sternlieb and associates[14,15] found the sign to be highly correlated with coronary atherosclerosis. Mehta and Hamby,[16] while noting a slightly greater proportion of ear creases among patients with coronary artery diseases, did not consider the difference to be significant. More recently, autopsy studies by Lichstein and colleagues[23] have shown a statistically significant correlation

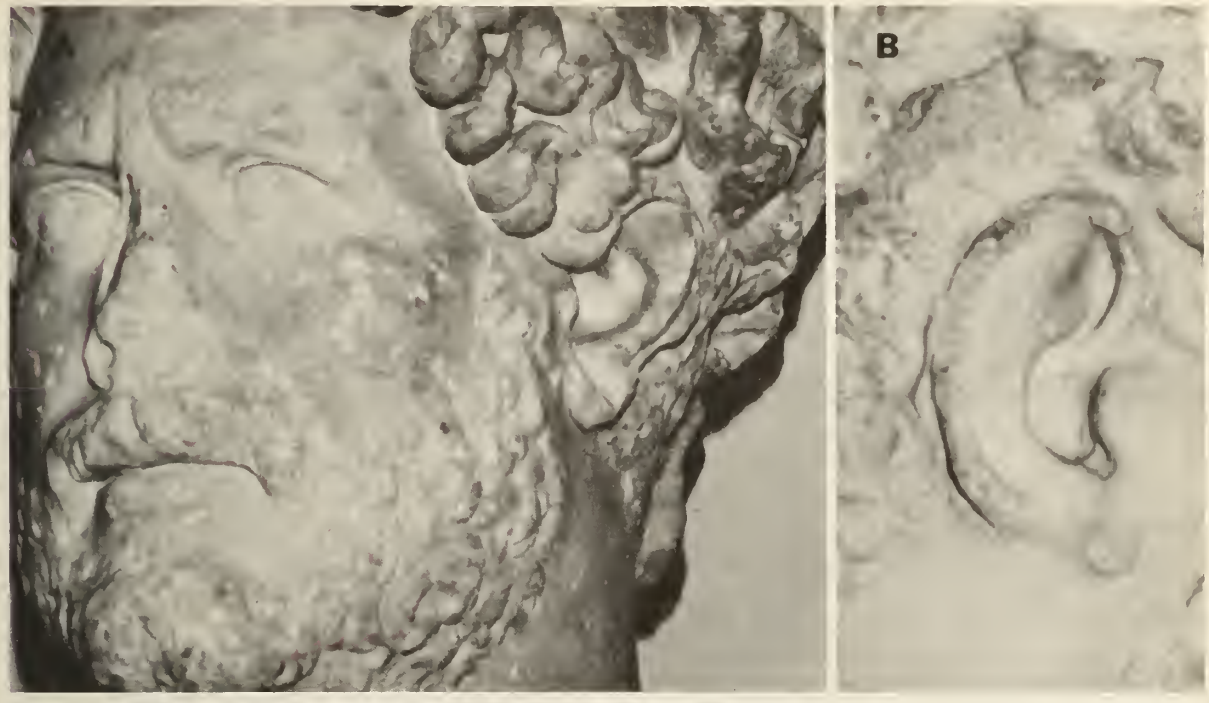

Figure 1.—Bust of Hadrian, Athens National Museum No. 3729, showing: **A** left and **B** right diagonal ear creases. (Photographed with permission and assistance from Dr. E. Raftopoulou, Sculpture Department, Athens National Museum.)

Figure 2.—Busts of Hadrian, Museo Nationale Romano. Both statues show bilateral diagonal ear creases.

of bilateral diagonal ear creases and occlusion of the coronary arteries. A comprehensive investigation of the earlobe crease in coronary heart disease recently published by Kaukola[24] offers additional support for the association.

A chance observation of prominent bilateral diagonal earlobe creases on a bust of Hadrian in the Athens National Museum (Figure 1) led me to seek other sculptures of Hadrian to determine how characteristic this feature was of the emperor. I was able to find two additional busts of Hadrian in the Museo Nazionale Romano in Rome and one in the Prado Museum in Madrid, all of which showed similar ear creases (Figure 2). In addition, published photographs of a bust of Hadrian in the Uffizi Gallery in Florence clearly depict the ear creases.[25] Roman portrait sculpture is considered to be highly accurate and detailed.[26-28] Because portrait sculptures of other Roman emperors and nobles in these museums do not possess the diagonal earlobe creases, if ear creases are depicted on these busts, they can be assumed to represent a true physical trait. In Hadrian's case, the bilateral diagonal ear creases in connection with clinical signs and symptoms suggestive of hypertension and congestive heart failure offer additional evidence in support of an underlying diagnosis of coronary artery disease.

Additional evidence supports the view that Hadrian died as a result of coronary atherosclerosis. Recently, Friedman and Rosenman[29] and collaborators[30] described a specific behavior pattern which they believe to be associated with increased susceptibility to coronary heart disease. Persons with this behavior pattern (type A) "are competitive, achievement-oriented, involved in multiple activities with deadlines, impatient with slowness in others, like to set a rapid work pace, and tend to be hostile and aggressive."

From the descriptions provided by Dio Cassius and the *Historia Augustae* of the temperament of Hadrian, the emperor appears to have possessed this behavior pattern. He is described as having "insatiable" ambition and interest in all conceivable pursuits. He declared that "there was nothing pertaining to peace or war, to imperial or private life, of which he was not cognizant." "He wrote, dictated, listened and, incredible as it seems, conversed with his friends at one and the same time."[3] Dio Cassius[2] notes that "Hadrian was jealous of all who excelled in any respect" and that "inasmuch as he wished to surpass everybody in everything, he hated those who attained eminence in any direction." And "although he was very deft at prose and at verse and accomplished in all the arts, yet he used to subject the teachers of these arts . . . to ridicule, scorn, and humiliation."[3] A modern historian, Wynne Williams,[31] analyzed existing fragments of Hadrian's administrative correspondence and concluded that "Hadrian's individuality is revealed in his letters to his subordinates rather than in formal correspondence with cities. The most striking characteristics are impatience with time wasting and anger at the corruption of justice or the evasion of public duties."

From these details it appears that Hadrian's temperament may be characterized as type A, which lends further support to the conclusion that his death was due to coronary atherosclerosis. This deduction should be tempered by the possibility that this behavior pattern may be a characteristic of all emperors.

Without additional information on the clinical and physical nature of Hadrian's condition and in the absence of modern laboratory test results, it is impossible to be certain of Hadrian's true illness. Nevertheless, classical literary and sculptural evidence, combined with recent clinical and epidemiologic findings that may help predict the presence of coronary heart disease, appear to offer a new insight into the death of this famous Roman emperor.

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Management of Behavioral Problems

THE PROBLEMS OF INFANTS up to 6 months old basically divide into two groups. First are those problems that are of incredible magnitude (the child with marasmus . . . children with severe mental retardation . . . children with severe impairment) . . . these are probably noticed very early on. The other problems . . . are practically never handled by psychiatrists—they are all handled by pediatricians, and they basically involve the misfit between the mother and the child. The failure of the mother to perceive children's cues . . . the expectations which are pitched higher than the child is able to handle.

—JAMES Q. SIMMONS, III, MD, *Los Angeles*

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CURRENT NEUROLOGY—Volume 1—Edited by H. Richard Tyler, MD, Professor of Neurology, Harvard Medical School; Head, Section of Neurology, Peter Bent Brigham Hospital, Boston; and David M. Dawson, MD, Associate Professor of Neurology, Harvard Medical School; Physician, Section of Neurology, Peter Bent Brigham Hospital, Houghton Mifflin Professional Publishers, Medical Division, Two Park St., Boston (02107), 1978. 499 pages, $29.00 (US), $37.50 (elsewhere).

This volume is primarily directed toward busy neurologists as a mechanism to help these physicians "remain up-to-date." The editors have proposed a yearly review similar to this volume covering the field of neurology in a two-to-three year cycle.

As with most multiauthored books, there is great variation in the quality of individual chapters. For example, the chapter on myasthenia gravis is well organized, highly informative and includes recent advances in the pathophysiology of the disorder. On the other hand, the chapter on multiple sclerosis, while containing the most recent etiologic theories, is poorly organized and rambling.

Some of the information presented is quite new and there has not been sufficient time to confirm the observations or to fully appreciate the overall significance of the information to the discipline of neurology. The chapter on Friedreich's and other hereditary ataxias demonstrates this problem clearly. The author attempts to reclassify the various dominantly inherited ataxias into a single disorder which he calls "dominant hereditary ataxia." This author utilized reports of HLA linkage in two families to support his proposed unifying classification. More recent reports have now shown multiple forms of dominantly inherited ataxia as there are some families in which there is HLA linkage (chromosome 6) and yet other families where no HLA system linkage was present. This more recent evidence supports the older classification systems that there are indeed different genetic forms of the dominantly inherited ataxias.

While this volume is directed towards neurologists there are certain chapters which would be of great value to generalists. This reviewer can highly recommend the following chapters: Parkinson's Disease, Transient Ischemic Attacks, and Hypertension and the Central Nervous System.

At the end of many of the chapters the editors present some new information of their own. The editors could have utilized their vast collective experience more effectively by discussing and clarifying certain aspects of the preceding chapter than by presenting these new topics.

The volume is handsomely presented but too expensive for a yearly review.

* * *

CURRENT NEUROLOGY—Volume 2—Houghton Mifflin Professional Publishers, Medical Division, Two Park St., Boston (02107), 1979. 531 pages, $34.00 (US), $42.50 (elsewhere).

Current Neurology—Volume 2 follows the initial publication of Volume 1 by approximately a year, as promised by the editors in the preface to Volume 1. The editors are to be congratulated; this was obviously a monumental task considering the number of contributors with which they had to deal.

The current volume contains a review of 16 new topics in addition to 10 shorter updates of topics covered in Volume 1. As a whole, the new reviews are reasonably well presented and cover a wide spectrum of topics from specific degenerative and neoplastic disorders to a proposed research project to clarify the possible role of mitochondrial dysfunction in a number of seemingly unrelated diseases. The chapters entitled "Valproate and the Management of Seizures" and "Evoked Potentials" are both excellent. The chapter entitled "Neuropsychologic Aspects of Aphasia" reflects the state of the art concerning the lack of understanding responsible for normal or disordered language.

The update chapters are relatively short and most of the references are quite recent. The amount of useful new information, however, is not commensurate with the amount of space devoted to these chapters. The editors' choice of this format is unfortunate because it requires the purchase of the entire series and constant referral to earlier volumes for these updates to be meaningful.

While *Current Neurology—Volume 2* is directed at neurologists particularly, internists and generalists will find the review chapters on "Intracerebral Hemorrhage," "Viral Diseases of the Nervous System," "The Heart and Neurologic Disorders" and "Metabolic Encephalopathy" particularly useful.

This volume is handsomely published, but too expensive for a yearly review.

DONALD F. FARRELL, MD
Associate Professor of Medicine (Neurology)
Associate Director for Biomedical Research
Child Development and Mental Retardation Center
University of Washington School of Medicine
Seattle

* * *

THE MANAGEMENT OF MEDICAL PRACTICE—John McCormick, MHA, Administrative Services, Mayo Clinic, Rochester, Minnesota; Ronald Lee Rushing, CPA, MBA, Director of Fiscal Services, Kelsey-Seybold Clinic, Houston; and W. Grayburn Davis, MD, Executive Vice President, American Group Practice Association, Alexandria, Virginia. Ballinger Publishing Company, 17 Dunster Street, Harvard Square, Cambridge, MA (02138), 1978. 388 pages, $20.00.

One of the most difficult problems every doctor in private practice has to face is how to manage a practice. Everyone comes out of training well enough prepared to deliver health care, but few of us acquire much knowledge along the way about the economic mechanisms involved. This book is an admirable, and I believe successful, attempt to present a great deal of information that most of us are forced to learn the hard way. Any doctor planning to go into the practice of medicine, whether it be solo, partnership, group, or even working for a governmental entity, would profit from reading this book. It goes into the day-by-day details of how to run an office, all the pertinent legal and accounting ramifications, how to set up the practice in the first place, how to choose the proper locale, and even how to figure out what might be the best sort of practice for you. The credentials of the writers seem good indeed; this is perhaps best substantiated by the fact that they present their views in clear, concise language, and simply enough (even with rather complex tax and accounting matters) that the average doctor should be well able to understand. Not only should doctors just entering private practice read this book, I believe that those of us still actively engaged in private practice can learn a great deal from reading it.

JOHN L. BENTON, MD
Los Angeles

in memoriam

California Medical Association

Baker, Frances, Burlingame. Died April 20, 1979 of heart disease, aged 84. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Dr. Baker was a retired member of the San Mateo County Medical Society.

Bauer, Julius, Beverly Hills. Died May 8, 1979 of heart disease, aged 91. Graduate of Medizinische Fakultät der Universität, Wien, 1910. Licensed in California in 1940. Dr. Bauer was a member of the Los Angeles County Medical Association.

Butler, Kenneth W., Madera. Died September 29, 1979 in Madera, aged 73. Graduate of the University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Dr. Butler was a retired member of the Fresno-Madera Medical Society.

Doersch, Earl A., Sacramento. Died October 11, 1979, aged 77. Graduate of the University of Wisconsin Medical School, Milwaukee, 1936. Licensed in California in 1944. Dr. Doersch was a member of the Sacramento County Medical Society.

Dunn, Seldon C., San Diego. Died October 20, 1979 in Athens, Greece of heart disease, aged 63. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1949. Licensed in California in 1958. Dr. Dunn was a member of the San Diego County Medical Society.

Ender, Kenneth Earl, Pinole. Died September 27, 1979 in Pinole, aged 47. Graduate of the University of Wisconsin Medical School, Madison, 1958. Licensed in California in 1959. Dr. Ender was a member of the Alameda-Contra Costa Medical Association.

Farley, Stanley E., Riverside. Died May 16, 1979 of malignant brain tumor, aged 61. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1945. Licensed in California in 1945. Dr. Farley was a retired member of the Riverside County Medical Association.

Harwood, Chad M., Orange. Died March 25, 1979 of heart disease, aged 73. Graduate of the University of Southern California School of Medicine, Los Angeles, 1935. Licensed in California in 1935. Dr. Harwood was a retired member of the Orange County Medical Association.

Hebard, Harold G., Long Beach. Died May 28, 1979 in Hong Kong, aged 78. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1925. Licensed in California in 1952. Dr. Hebard was a member of the Los Angeles County Medical Association.

Henderson, Ernest W., Walnut Creek. Died November 2, 1979 in Walnut Creek, aged 78. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Dr. Henderson was a retired member of the Alameda-Contra Costa Medical Association.

Howe, Ralph D., Redwood City. Died November 1, 1979 in Redwood City, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1929. Licensed in California in 1929. Dr. Howe was a retired member of the San Mateo County Medical Society.

Johnson, Herbert H., jr., Burlingame. Died October 13, 1979 in Burlingame of heart disease, aged 66. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1938. Licensed in California in 1938. Dr. Johnson was a member of the San Mateo County Medical Society.

Kass, Robert H., Fresno. Died October 15, 1979 in Fresno of cerebrovascular accident, aged 59. Graduate of the University of Illinois College of Medicine, Chicago, 1949. Licensed in California in 1950. Dr. Kass was a member of the Fresno-Madera Medical Society.

Kent, Glen W., Walnut Creek. Died October 30, 1979 in Walnut Creek, aged 66. Graduate of the University of California Medical School, Berkeley-San Francisco, 1942. Licensed in California in 1942. Dr. Kent was a retired member of the Alameda-Contra Costa Medical Association.

Kernkamp, Leila M., Whittier. Died September 7, 1979, aged 84. Graduate of the University of Minnesota Medical School, Minneapolis, 1927. Licensed in California in 1930. Dr. Kernkamp was a retired member of the Los Angeles County Medical Association.

Kimura, Samuel Jiro, San Francisco. Died October 15, 1979 in Granada, Spain of injuries received in automobile accident, aged 67. Graduate of the University of California Medical School, Berkeley-San Francisco, 1941. Licensed in California in 1941. Dr. Kimura was a member of the Alameda-Contra Costa Medical Association.

Lavelle, Joseph P., San Francisco. Died November 1, 1979 in Hillsborough of heart disease, aged 56. Graduate of the Creighton University School of Medicine, Omaha, 1952. Licensed in California in 1954. Dr. Lavelle was a member of the San Francisco Medical Society.

Marks, Harold, Stockton. Died April 30, 1979 of diffuse histocytic lymphoma, aged 67. Graduate of the University of Illinois College of Medicine, Chicago, 1936. Licensed in California in 1947. Dr. Marks was a retired member of the San Joaquin County Medical Society.

McGourty, David P., San Juan Capistrano. Died May 12, 1979 of myocardial infarction, aged 79. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1927. Licensed in California in 1950. Dr. McGourty was a retired member of the Orange County Medical Association.

Roehm, Edgar A., Los Angeles. Died March 31, 1979 of heart disease, aged 72. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1923. Licensed in California in 1936. Dr. Roehm was a member of the Los Angeles County Medical Association.

Rosenberg, Maurice W., Los Angeles. Died April 2, 1979, aged 79. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1922. Licensed in California in 1922. Dr. Rosenberg was a member of the Los Angeles County Medical Association.

Shaw, Gerald W., Santa Monica. Died October 22, 1979 in Santa Monica of heart disease, aged 77. Graduate of Harvard Medical School, Boston, 1928. Licensed in California in 1936. Dr. Shaw was a member of the Los Angeles County Medical Association.

Spencer, Reuel M., Newport Beach. Died May 17, 1979 of congestive heart failure, aged 84. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1919. Licensed in California in 1919. Dr. Spencer was a retired member of the Los Angeles County Medical Association.

Spritzler, Ramon J., Los Angeles. Died in October 1978, aged 64. Graduate of the Hahnemann Medical College and Hospital, Philadelphia, 1939. Licensed in California in 1945. Dr. Spritzler was a member of the Los Angeles County Medical Association.

Steele, Muriel R., San Francisco. Died October 27, 1979 of cancer, aged 49. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1957. Licensed in California in 1959. Dr. Steele was a member of the San Francisco Medical Society.

Sullivan, Harry J., Redwood City. Died April 20, 1979 at Stanford University Hospital of myocardial infarct, aged 57. Graduate of the Creighton University School of Medicine, Omaha, 1946. Licensed in California in 1947. Dr. Sullivan was a member of the San Mateo County Medical Society.

Truax, Hugh C., Temple City. Died September 4, 1979, aged 63. Graduate of the University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1943. Dr. Truax was a member of the Los Angeles County Medical Association.

Wisotsky, Edward I., Los Angeles. Died May 31, 1978 of cancer, aged 63. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1940. Licensed in California in 1940. MD degree from California College of Medicine, 1962. Dr. Wisotsky was a member of the Los Angeles County Medical Association.

Washington State Medical Association

Batchelder, Wendell Webster, Seattle. Died October 1, 1979, aged 52. Graduate of Harvard Medical School, Boston, 1955. Licensed in Washington in 1967. Dr. Batchelder was a member of the King County Medical Society.

Lee, Harry Philip, Sun City, Arizona. Died September 28, 1979, aged 79. Graduate of the University of Iowa College of Medicine, Iowa City, 1937. Licensed in Washington in 1938. Dr. Lee was a retired member of the Spokane County Medical Society.

Maddison, Frank R., Tacoma. Died August 24, 1979, aged 77. Graduate of Northwestern University Medical School, Chicago, 1926. Licensed in Washington in 1928. Dr. Maddison was a retired member of the Pierce County Medical Society.

Murphy, Norman W., Seattle. Died September 21, 1979, aged 77. Graduate of the University of Colorado School of Medicine, Denver, 1926. Licensed in Washington in 1929. Dr. Murphy was a member of the King County Medical Society.

Reimer, Herbert W., Seattle. Died September 1, 1979, aged 64. Graduate of the Chicago College of Osteopathic Medicine, 1943. Licensed in Washington in 1945 (DO). Dr. Reimer was a retired member of the King County Medical Society.

Riley, John B., Seattle. Died August 12, 1979, aged 72. Graduate of the University of Minnesota Medical School, Minneapolis, 1934. Licensed in Washington in 1940. Dr. Riley was a member of the King County Medical Society.

Sleep, Somers R., Tacoma. Died August 25, 1979, aged 78. Graduate of the University of Oregon Medical School, Portland, 1931. Licensed in Washington in 1933. Dr. Sleep was a member of the Pierce County Medical Society.

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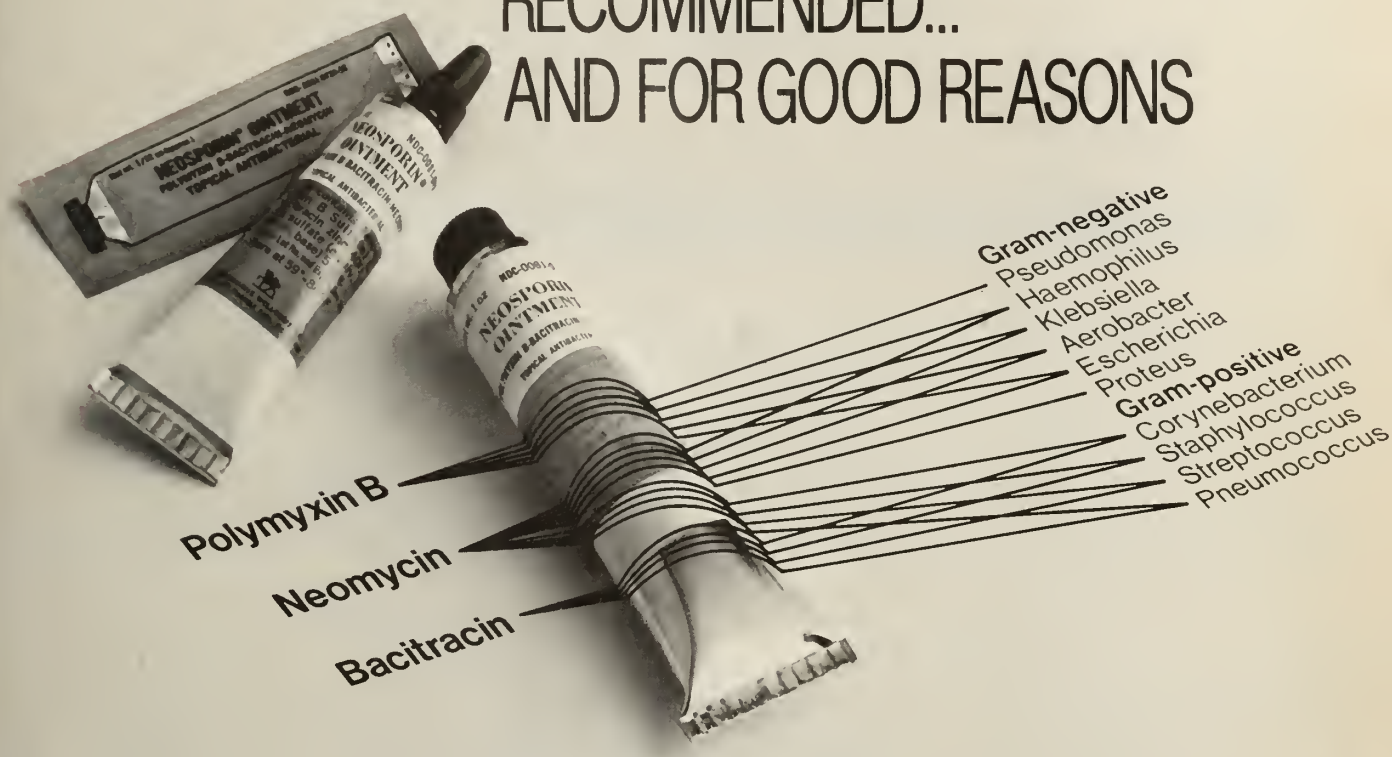

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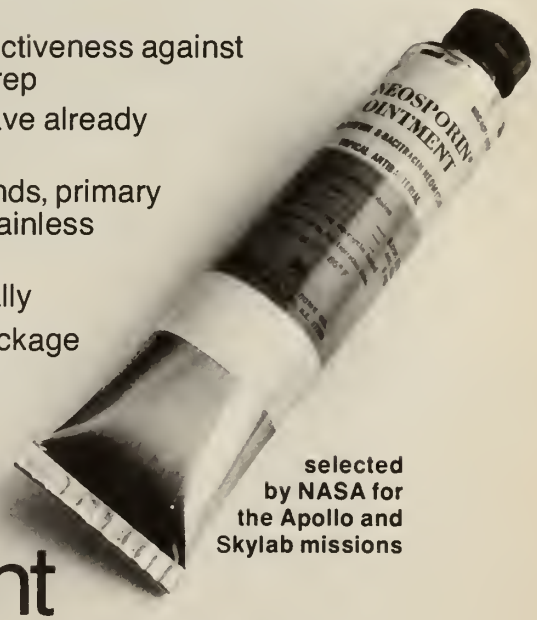

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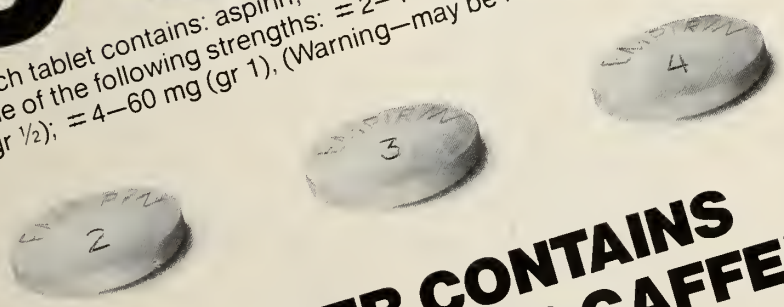

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(Continued from Page 22)

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PEDIATRICIAN, university-trained, licensed in California, seeks group practice or clinic position in San Francisco/Bay Area. Reply Box 6084, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ABORTING AMERICA—Bernard N. Nathanson, MD, and Richard N. Ostling. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1979. 320 pages, $10.00.

AGAINST OURSELVES—Disorders From Improvements Under the Organic Limitedness of Man—D. G. Garan, PhD, JUD, LLD, Philosophical Library, Inc., 15 East 40th Street, New York City (10016), 1979. 310 pages, $9.75.

COOKING CREATIVELY FOR YOUR DIABETIC CHILD—Caroline Hastings Babington. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1979. 224 pages, $8.95.

CURRENT SURGICAL DIAGNOSIS & TREATMENT—Fourth Edition—J. Englebert Dunphy, MD, Professor of Surgery Emeritus, University of California, San Francisco; Lawrence W. Way, MD, Professor of Surgery, University of California, San Francisco, Chief of Surgical Service, San Francisco Veterans Administration Medical Center; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1979. 1,162 pages, $19.00.

CURRENT TRENDS IN TUMOR IMMUNOLOGY—Edited by Soldano Ferrone, Dept. of Molecular Immunology, Scripps Clinic and Research Foundation, La Jolla, California; Sergio Gorini, Fondazione Internazionale, Florence, Italy; Ronald B. Herberman, Laboratory of Immunodiagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD; and Ralph A. Reisfeld, Dept of Molecular Immunology, Scripps Clinic and Research Foundation, La Jolla. Garland STPM Press, 136 Madison Avenue, New York City (10016), 1979. 381 pages, $37.50.

ELECTRON MICROSCOPY OF THE KIDNEY IN RENAL DISEASE AND HYPERTENSION—Anil K. Mandal, MD, Director, Renal Electron Microscopy Laboratory, and Staff Physician, Medical Service, Veterans Administration Medical Center, and Associate Professor of Medicine, University of Oklahoma College of Medicine, Oklahoma City; with the collaboration of James E. Wenzl, MD, Professor and Chairman, Department of Pediatrics, Children's Memorial Hospital and University of Oklahoma College of Medicine. Plenum Publishing Corporation, 227 West 17th Street, New York City (10011), 1979. 452 pages, $32.50.

EVALUATION AND MANAGEMENT OF ALLERGIC AND ASTHMATIC DISEASES—Edited by M. Eric Gershwin, MD, and Stephen M. Nagy, Jr., MD, Section of Rheumatology-Allergy, Department of Medicine, University of California, Davis, School of Medicine, Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1979. 284 pages, $16.50.

EVALUATION IN MEDICAL EDUCATION: Past, Present, Future—Thomas Samph, PhD, Associate Director, Dept. of Research and Development, National Board of Medical Examiners; and Bryce Templeton, MD, Principal Investigator, Comprehensive Qualifying Evaluation Program, National Board of Medical Examiners. Ballinger Publishing Company, Cambridge, MA (02138), 1979. 331 pages, $22.50.

FROM MAN TO MAN—Henry Ritter, Jr., MD; with Owen Spann. Harper & Row, Publishers, 1700 Montgomery St., San Francisco (94111), 1979. 167 pages, $8.95.

IMMUNOLOGIC MECHANISMS OF RENAL DISEASE—Volume 3 of CONTEMPORARY ISSUES IN NEPHROLOGY—Guest Editor: Curtis B. Wilson, MD, Member, Department of Immunopathology, Research Institute of Scripps Clinic, La Jolla, California; Series Editors: Barry M. Brenner, MD, Samuel A. Levine Professor of Medicine, Harvard Medical School; Director, Renal Division and Laboratory of Kidney and Electrolyte Physiology, Peter Bent Brigham Hospital, Boston; and Jay H. Stein, MD, Professor and Chairman, Department of Medicine; Director, Division of Renal Diseases, the University of Texas Health Science Center at San Antonio. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1979. 371 pages, $27.50.

LAST LETTER TO THE PEBBLE PEOPLE: "Aldie Soars"—Virginia Hine, MA; with foreword by Elizabeth Kübler-Ross, MD. Unity Press, 113 New Street, Santa Cruz, CA (95060), 1977, 1979. 158 pages, $5.95 (paperback).

THE NERVOUS SYSTEM—Second Edition—William F. Ganong, MD, Professor and Chairman, Department of Physiology, University of California School of Medicine, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1979. 243 pages, $11.00.

NOT IN MY TIME—The Story of a Doctor—Dr. Sigismund Peller. Philosophical Library, Inc., 15 East 40 Street, New York City (10016), 1979. 374 pages, $15.00.

THE PSYCHOGENIC BIOCHEMICAL ASPECTS OF CANCER—Harold E. Simmons. Psychogenic Disease Publishing Company, P.O. Box 19098, Sacramento, CA (95819), 1979. 316 pages, $9.95 (paperback).

TECHNIQUES IN SKIN SURGERY—Ervin Epstein, MD, Emeritus Associate Clinical Professor of Dermatology, University of California, San Francisco, School of Medicine; and Ervin Epstein, Jr., MD, Associate Clinical Professor of Dermatology, Assistant Research Dermatologist, University of California, San Francisco, School of Medicine. Lea & Febiger, 600 Washington Square, Philadelphia (19106), 1979. 203 pages, $18.00.

UNDERSTANDING CANCER—Edited by Mark Renneker, MD, Fourth Year Medical Student, University of California, San Francisco, American Cancer Society Volunteer; and Steven Leib, MD, Intern in Family Practice, University of California, Los Angeles, Center for the Health Sciences, American Cancer Society Volunteer. Bull Publishing Co., P.O. Box 208, Palo Alto, CA (94302), 1979. 463 pages, $19.95 (cloth), $12.95 (paperback).

THE VITAMIN BOOK—Rich Wentzler. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1979. 224 pages, $4.95 (paperback).

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Membership is open to qualified physicians from all States. For information, write to the Society at 731 Market Street, San Francisco, CA 94103.

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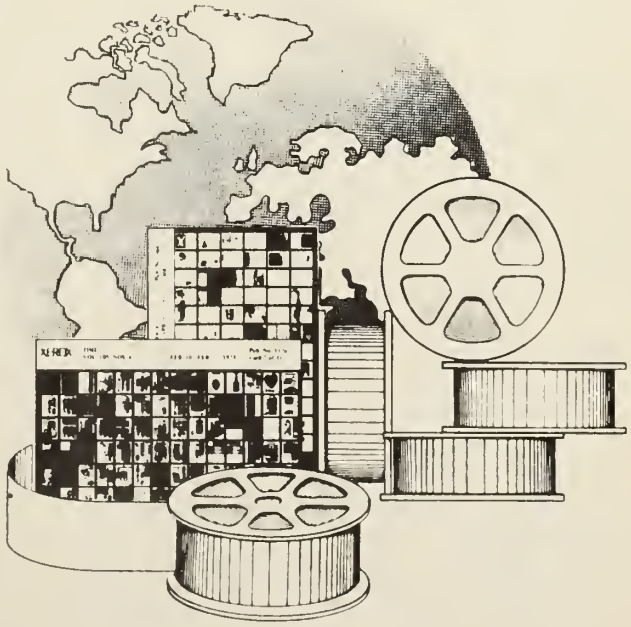

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ANESTHESIOLOGY

January 25-27—**Pediatric Anesthesiology—18th Clinical Conference.** Childrens Hospital at Marriott, Los Angeles. Friday-Sunday. 15 hrs. $160. Contact: Wayne Herbert, MD, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

February 7-10—**7th Neonatal and Infant Respiratory Symposium.** Ohio State Univ., Dept. of Anesthesiology, at Marriott, Los Angeles. Thursday-Sunday. Contact: John S. McDonald, MD, Dept. of Anesthesiology, OSU, 410 W. 10th Ave., Columbus, OH 43210. (614) 422-5591.

February 13—**Local Anesthesia and Regional Blocks.** See Emergency Medicine, February 13.

March 30-April 5—**Obstetric Anesthesia.** Ohio State University, Dept. of Anesthesiology, at Sheraton Waikiki Hotel, Oahu, Hawaii. One week. Contact: John S. McDonald, MD, Dept. of Anesthesiology, OSU, 410 W. 10th Ave., Columbus, OH 43210. (614) 422-5591.

CANCER

January 16—**Testicular Tumors.** Hospital of the Good Samaritan at Biltmore, Los Angeles. Wednesday. Contact: Janie Sternal, Cont. Med. Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

January 19—**Advances, Treatments and Modern Techniques in Leukemia.** S.F. Regional Cancer Foundation and Leukemia Soc. of America at Fireman's Fund Bldg., San Francisco. Saturday. Contact: Dr. Terry Sheehy, S.F. Reg. Cancer Fndn., 14th and Lake, San Francisco 94118. (415) 211-2132.

January 25-26—**Cancer Update.** Peralta Hospital at Goodman's Hall, Oakland. Friday-Saturday. 10 hrs. Contact: Education and Training Dept., Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900.

February 1-3—**Living with Childhood Cancer.** UCSD at Bahia Hotel, San Diego. Friday-Sunday. 14 hrs. $90.

February 23—**Current Trends in Lung Cancer Diagnosis and Management—6th Annual Pulmonary Symposium.** USC and Inter-Community Hosp., Covina, at Calif. State Univ., Pomona. Saturday. 6 hrs. Contact: Linda Arbiter, MPH, Med. Ed. Coordinator, Inter-Community Hosp., 303 N. 3rd Ave., Covina 91723.

March 14—**Cancer of the Endometrium.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

March 15-16—**Pharmaceutical Aspects of Cancer Care—15th Annual San Francisco Cancer Symposium.** West Coast Cancer Foundation and American Cancer Soc. at Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: West Coast Cancer Foundation, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

EMERGENCY MEDICINE

January 21-25—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 21-25—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

January 25-27—**Advanced Cardiac Life Support Provider, Recertification and Instructor Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: Sheila Tobin, Dept. of Cont. Ed., EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

February 11-14—**Emergency Medicine 1980.** UCD at Hyatt Lake Tahoe, Incline Village. Monday-Thursday. 18 hrs. $175.

February 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

February 13—**Local Anesthesia and Regional Blocks.** Los Robles Hosp. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at Los Robles Reg. Med. Ctr., Thousand Oaks. Wednesday; 8:00 p.m. 1½ hrs. CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

February 14-15—**Maxillofacial Trauma.** See Surgery, February 14-15.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

March 9-15—**Mammoth Mountain Emergency Medicine Ski Conference.** UCI and Orange Co. Emergency Dept. Nurses' Assn. at Mammoth Lakes. Sunday-Saturday. 24 hrs. Cat. I CMA. ACEP; 24 elective credit hrs. AAFP. $250. Contact: Daniel Abbott, MD, Med. Conf., Inc., P.O. Box 52-B, Newport Beach 92662. (714) 642-7080.

March 17-21—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

April 12-13—**Symposium on Survival: An Analysis of Disaster Planning.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

April 12-19—**Emergency Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

April 17—**Infectious Disease for Emergency Physicians.** Goleta Valley Community Hospital and Assn. for Emergency Physicians for Ventura and Santa Barbara Counties at Goleta Valley Hosp., Santa Barbara. Thursday. 1½ hrs. CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

April 21-25—**Postgraduate Institute for Emergency Physicians,** Symposium I. UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

May 5-9—**Emergency Surgical Problems.** White Memorial Medical Center and LLU at Honolulu and Maui, Hawaii. Monday-Friday. 24 hrs. $200. Contact: Dir., Cont. Med. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000, ext. 1460.

May 11-17—**Modern Trends in Emergency Medicine.** Univ. of Hawaii, John A. Burns School of Medicine, Hawaii. One week. Contact: Delia M. Chang, CME, Univ. of Hawaii, John A. Burns Sch. of Medicine, 1960 East-West Rd., Honolulu 96822.

May 14—**Emergency Medicine Symposium.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

May 19-23—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 40 hrs. $300.

MEDICINE

January 20-24—**Angiography and Vascular Disease.** UCSD at Vacation Village, San Diego. Sunday-Thursday. 26 hrs. $325.

January 26—**Asthma and Allergies.** UCLA. Saturday.

January 26-27—**The Healing Brain.** UCSF Cont. Ed. Health Sciences and Institute for the Study of Human Knowledge at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 1308 3rd Ave., San Francisco 94143. (415) 666-2894.

January 26-February 2—**Nephrology.** USC at Princeville at Hanalei, Kauai, Hawaii. One week.

January 28-30—**Standards and Controversies in Pulmonary Function Testing: 1980.** Calif. Thoracic Society at Sheraton Harbor Island Hotel, San Diego. Monday-Friday. $250. Contact: Anna B. Roberts, CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

January 31-February 1—**Hypertension: Advances in Treatment.** American Heart Assn., Orange Co. Chap., at Registry Hotel, Irvine. Thursday-Friday. Contact: AHA, Orange Co. Chap., 1043 Civic Center Dr. West, Santa Ana 92703. (714) 547-3001.

January 31-February 2—**Fundamentals of Echocardiography—An Introductory Course for Clinicians.** American College of Cardiology at Century Plaza, Los Angeles. Thursday-Saturday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 1-3—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Bahia Hotel, San Diego. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

February 2—**Pediatric Dermatology Seminar.** STAN. Saturday. Contact: Paul H. Jacobs, MD, Dept. of Derm., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

February 4-6—**American College of Physicians—Hawaii Regional Meeting.** Tripler U.S. Army Hospital, Honolulu. Monday-Wednesday. Contact: James J. Ball, MD, FACP, 1319 Punahou St., #1190, Honolulu 96826.

February 7-9—**Tri-State Symposium on Clinical Cardiology.** American Heart Assn.'s Council on Clinical Cardiology; AHA, Greater Los Angeles, Arizona and New Mexico Affiliates, at Disneyland Hotel, Anaheim. Thursday-Saturday. 15 hrs. $200, Heart Assn. member; $250, nonmember. Contact: LaVerna Titus, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

February 13—**Chronic Obstructive Pulmonary Disease.** LLU. Wednesday. 4 hrs.

February 13-15—**Advances in Neurology.** UCSF. Wednesday-Friday.

February 13-15—**Cardiovascular Disease—1980: Advances in Diagnosis and Management.** American College of Cardiology at Vacation Village, San Diego. Wednesday-Friday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 16—**5th Annual Liver Conference, Cholestasis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. $105. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave, Long Beach 90801. (213) 595-3811.

February 16-17—**Practical Gastroenterology for Primary Care Physicians.** UCLA at Miramar-Sheraton, Santa Monica. Saturday-Sunday. 12 hrs. $160.

February 16-23—**Clinical Allergy.** Univ. of Hawaii, John A. Burns Sch. of Med. at Maui Surf Hotel, Maui, Hawaii. One week. 28 hrs. $250. Contact: Delia M. Chang, Cont. Med. Ed., Univ. of HI, John A. Burns Sch. of Med., 1960 East-West Rd., Honolulu 96822.

February 21-24—**Federation of Western Societies of Neurological Science—Annual Meeting.** Biltmore Hotel, Santa Barbara. Thursday-Sunday. Contact: J. Carroll Ramseyer, MD, EEG/EMG Laboratory, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017.

February 22-23—**Medical Knowledge Self Assessment II.** American College of Physicians and PMC at Hyatt Regency, San Francisco. Friday-Saturday. 12 hrs. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

February 22-23—**Rehabilitation in Neurological Dysfunction.** PMC at Mark Hopkins Hotel, San Francisco. Friday-Saturday. 9 hrs. $135.

March 5—**Thyroid '80.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. Contact: Janie Sternal, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

March 7—**6th Annual Diabetes Program.** UCD at Red Lion Motor Inn, Sacramento. Friday. 6½ hrs.

March 7-9—**Northern California-Nevada Regional Meeting, American College of Physicians.** Doubletree Inn, Monterey. Friday-Sunday. Contact: Ralph O. Wallerstein, MD, 3838 California St., San Francisco 94118.

March 11-13—**Pulmonary Complications of Trauma.** Alta Bates Hospital, Calif. Society for Respiratory Therapy, American Lung Assn. of Alameda Co. at Hyatt Lake Tahoe, Incline Village. Tuesday-Thursday. 9 hrs. Contact: Claudia F. Read, Medical Ed., Alta Bates Hosp., 3001 Colby, Berkeley 94705. (415) 845-7110, ext. 2031.

March 13-16—**Pediatric Cardiology—A Growing Concern: What the Primary Care Physician Should Know.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Sunday. 11 hrs.

March 15-16—**Human Lymphocyte Antigens.** UCSD at Hilton, San Diego. Saturday-Sunday.

March 16-19—**Basic Cardiology for the Primary Care Physician.** UCSF at Yosemite. Sunday-Wednesday.

March 21-23—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Jack Tar Hotel, San Francisco. Friday-Sunday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

March 24-26—**4th Annual Review and Update of the Immunology and Clinical Practice of Allergy.** USCD at Hilton, San Diego. Monday-Wednesday. 20 hrs. $225.

March 24-April 4—**Intensive Review of Internal Medicine.** USC. Two weeks.

March 26-28—**Endocrine Glands in Health and Disease.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday.

March 29-April 5—**Infectious Diseases.** Univ. of Washington School of Medicine at Naniloa and Kona Surf Hotels, Hilo, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 7-16—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 9—**Cardiovascular Disease.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Memorial Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

April 9—**Asthma in Childhood.** See Pediatrics, April 9.

April 9-June 11—**Practical Dermatology for the Practicing Internist.** UCLA. 10 Wednesday evenings. 20 hrs.

April 10-13—**Current Concepts and Advances in Diagnosis, Management and Prevention of Cardiac and Cardiopulmonary Diseases.** American Medical Assn. and American College of Cardiology at Los Angeles. Contact: AMA, 535 N. Dearborn, Chicago 60610. (312) 751-6000.

April 12-13—**Pediatric Dermatology.** UCLA. Saturday-Sunday.

April 12-19—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

April 25-27—**New Concepts in Clinical Electrocardiography.** American College of Cardiology at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 26-27—**Practical Rheumatology.** UCLA. Saturday-Sunday.

April 28-30—**Pediatric Dermatology.** STAN at Rancho Mirage. Monday-Wednesday. 18 hrs. $195.

May 2-4—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Sunday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

May 2-4—**Headache Management: Therapeutic Workshops.** UCLA at Newporter Inn, Newport Beach. Friday-Sunday.

May 3—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

May 9—**Asthma.** UCD. Friday.

May 15-17—**Acute Myocardial Infarction.** PMC at St. Francis Hotel, San Francisco. Thursday-Saturday. 15 hrs.

May 16-18—**Cardiac Rehabilitation.** International Medical Education Corp. at Jack Tar Hotel, San Francisco. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

May 19-24—**4th Bi-Annual Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday.

May 30—**Team Approach to Arthritis.** PMC and Arthritis Foundation. Friday. 6 hrs. $85.

OBSTETRICS AND GYNECOLOGY

January 20-23—**Obstetrics-Gynecology Update.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Wednesday. 20 hrs.

January 21-25—**Ob/Gyn Review.** USC. Monday-Friday.

January 23-26—**Clinical Obstetrics and Gynecology and Histological Pathology.** UCI and Women's Hospital of Long Beach at Newporter Inn, Newport Beach. Wednesday-Saturday. 26 hrs. $250. Contact: Prog. Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

February 9-10—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. 10 hrs. $70. Contact: Miss Dee Davis, Exec. Sec., 5820 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

March 12—**Vaginitis.** LLU. Wednesday. 4 hrs.

March 14-15—**25th Annual Postgraduate Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Shirley Gach, SCPMG, Education and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4242.

March 22-23—**Contraception: Current Research and Multidisciplinary Applications.** See Of Interest To All, March 22-23.

May 12-14—**Recent Advances in Ob/Gyn.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

May 16-18—**Ob/Gyn.** UCLA at Ojai Valley Inn, Ojai. Friday-Sunday. 12 hrs. $300.

PEDIATRICS

January 27-30—**Fifth Annual Winter Ski and Study Symposium.** American Academy of Pediatrics, Calif. Chap. 2, at Mammoth Mountain. Sunday-Wednesday. 11 hrs. $150, members; $175, nonmembers. Contact: AAP, P.O. Box 2134, Inglewood 90305.

February 2—**Pediatric Dermatology Seminar.** See Medicine, February 2.

February 4-6—**Pediatric Nephrology and Urology.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

February 7-10—**7th Neonatal and Infant Respiratory Symposium.** See Anesthesiology, February 7-10.

February 9-10—**The Health of the Young and the Development of Sexuality and Gender.** UCSF Cont. Ed. Health Sciences at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

February 21-23—**Practical Orthopedics for the Pediatrician.** Children's Hospital Medical Center of Northern Calif. at Sahara Tahoe Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, Med. Staff Office, Children's Hosp. Med. Ctr., 51st and Grove Sts., Oakland 94609. (415) 654-5600, ext. 215.

February 23—**Pediatric Review.** UCLA. Saturday.

March 5-7—**Pediatric Pulmonary Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 8—**Adolescent Medicine.** UCLA. Saturday.

March 13-16—**Pediatric Cardiology.** See Medicine, March 13-16.

April 4-5—**Pediatric Topics 1980.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 9 hrs. $80.

April 9—**Asthma in Childhood.** LLU. Wednesday. 4 hrs. $30.

April 11-12—**Pediatric Symposium—22nd Annual.** So. Calif. Permanente Medical Group at Sheraton Hotel, Anaheim.

Friday-Saturday. Contact: Shirley Gach, Ed. and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

April 12-13—**Pediatric Dermatology.** See Medicine, April 12-13.

April 28-30—**Pediatric Dermatology.** See Medicine, April 28-30.

May 3—**Pediatric Dermatology Seminar.** See Medicine, May 3.

May 5-9—**Pediatric Review—10th Annual.** USC. Monday-Friday.

May 7-9—**Care of the Sick Newborn.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 18 hrs. $130. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 8-10—**Annual Pediatrics Course.** UCSF at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

May 10-17—**Pediatric Workshop.** USC at Royal Lahaina, Maui, Hawaii. One week.

PSYCHIATRY

January 18-20—**Brief Psychotherapy.** UCSF. Friday-Sunday.

January 26-27—**The Healing Brain.** See Medicine, January 26-27.

January 27-February 1—**Midwinter Program in Continuing Education for Psychiatrists—6th Annual.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. 26 hrs. $200.

February 2—**Dealing With Depression.** UCLA. Saturday.

February 6-9—**Update in Psychiatry: Psychopharmacology.** UCSD at Vacation Village, San Diego. Wednesday-Saturday. 16 hrs. $200.

February 9—**Childhood Experiences and Adult Behavior.** No. Calif. Psychiatric Assn. and McAuley Institute at St. Mary's Hosp., San Francisco. Saturday. 3 hrs. Contact: George L. Ponomareff, MD, 2457 Grove Way, Suite 102, Hayward 94546.

February 9-10—**Sexual Therapy.** UCLA. Saturday-Sunday.

March 15—**The Void—Treatment of a Narcissistic Patient.** No. Calif. Psychiatric Society and McAuley Institute at St. Mary's Hospital, San Francisco. Saturday. 3 hrs. $15. Contact: George L. Ponomareff, MD, 2457 Grove Way, Suite 102, Hayward 94546.

March 21-23—**Narcissism—A Multidimensional View.** UCSF. Friday-Sunday.

April 12-13—**Intellect and Illness.** UCLA at Palo Alto. Saturday-Sunday.

May 5-9—**American Psychiatric Association.** Hilton, San Francisco. Monday-Friday. Contact: APA, 1700 18th St. NW, Washington, DC 20009.

RADIOLOGY AND PATHOLOGY

January 23-25—**7th Annual Genitourinary Pathology Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 23-26—**Clinical Obstetrics and Gynecology and Histological Pathology.** See Obstetrics and Gynecology, January 23-26.

January 25-27—**32nd Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Nathan Green, MD, 15107 Vanowen St., Van Nuys 91405.

January 26-27—**Modern Gastrointestinal Radiologic Techniques for Practicing Physicians.** UCSF at Fairmont, San Francisco. Saturday-Sunday. 13 hrs. $200.

January 28-February 1—**Computed Tomography, Ultrasound and X-Ray—An Integrated Approach.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 32 hrs. $295.

January 30-February 1—**Genito-Urinary Pathology—7th Annual Course.** Memorial Hospital Medical Center-UCI Center

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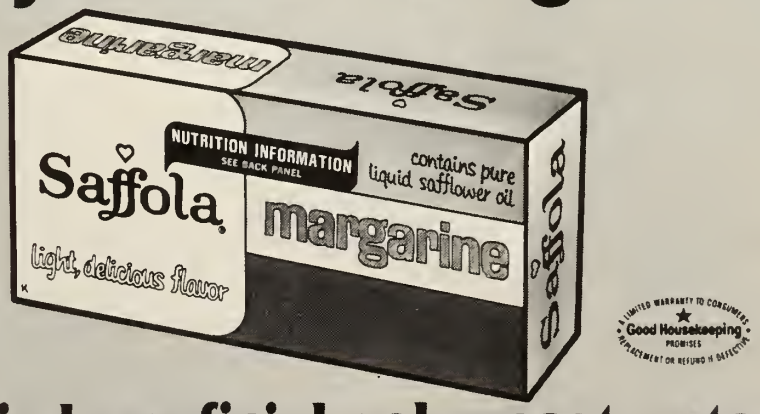

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MARCH 7-8
Ophthalmology Update I
APRIL 18-19
Workshop on Orthopedic Injuries
APRIL 21-25
1980 Family Practice Review
MAY 1-2
Therapeutic Drug Monitoring
MAY 9-10
Combined Otolaryngologic/Orthognathic Symposium
MAY 15-17
Acute Myocardial Infarction
MAY 15-17
Nasal Plastic and Reconstructive Surgery
MAY 30
Arthritis: The Team Approach to Diagnosis and Treatment
JUNE 6-7
Ophthalmology Update II
JUNE 19-20
Highlights of Ophthalmology
JUNE 20-21
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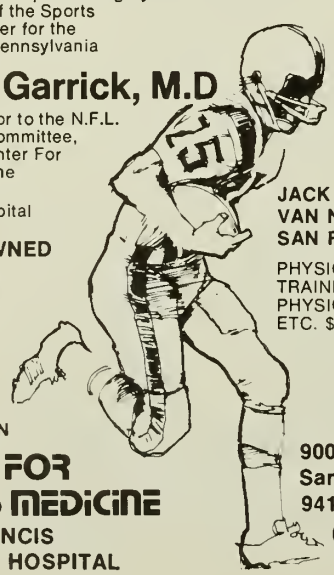

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for Health Education, Long Beach. Wednesday-Friday. 22½ hrs. $220. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 1-3—**Neuroradiology.** UCSF at Fairmont, San Francisco. Friday-Sunday. 20 hrs. $190.

February 14—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 22—**Practical Laboratory Mycobacteriology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 27-29—**Sierra Radiology Conference—Radiology of Problems in Clinical Medicine.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at Sahara Tahoe Hotel, South Lake Tahoe. Wednesday-Friday. 18 hrs. $215. Contact: Michael H. Reid, PhD, MD, Prog. Dir., Sacramento Radiology Research and Education Foundation, P.O. Box 161112, Sacramento 95816.

March 1-2—**Concepts and Controversies in Cardiopulmonary Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 11 hrs. $150.

March 3-7—**Diagnostic Radiology.** UCSF. Monday-Friday.

March 8-9—**A Practical Course in B-Scan Ultrasound.** UCSF. Saturday-Sunday.

March 13—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 10—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 13-18—**American Association of Pathologists.** Anaheim. Sunday-Friday. Contact: AAP, 9650 Rockville Pike, Bethesda, MD 20014.

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SURGERY

January 18-19—**2nd Annual Postgraduate Course in Surgery.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 12 hrs.

January 21-24—**Assembly in Surgery.** UCSD at Islandia Hyatt House, San Diego. Monday-Thursday. 28 hrs.

January 22-June 14—**Recent Advances in Surgical Science.** UCLA at Wadsworth VA Hospital, Los Angeles. One evening/month.

January 27-30—**21st Annual Theodor Billroth Course in Surgical Anatomy.** LLU. Sunday-Wednesday. 32 hrs. $250.

January 31-February 2—**Calculi.** American Urological Assn. at San Francisco. Wednesday-Friday. Contact: Office of Education, AUA, P.O. Box 1129, Aspen, CO 81611. (303) 925-2018.

February 1-3—**National Symposium on Hair Replacement Surgery.** Am. Academy of Facial Plastic and Reconstructive Surgery and Am. Soc. for Dermatologic Surgery at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. 19 hrs. $475. Contact: AAFPRS, 70 W. Hubbard St., Suite 202, Chicago 60610.

February 6-8—**Glaucoma.** UCSF at St. Francis Hotel, San Francisco. Wednesday-Friday. 16 hrs. $225.

February 7-9—**Vascular Surgery.** UCSF. Thursday-Saturday.

February 8-9—**Cataract Surgery and Intraocular Lenses: Planned Extracapsular, Phacoemulsification and Intracapsular Techniques.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $450. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

February 14-15—**Maxillofacial Trauma.** UCSF at Fairmont Hotel, San Francisco. Thursday-Friday. 15 hrs. $200.

March 1—**Corneal-External Ocular Disease Surgery Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

March 7-8—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

March 15-19—**Controversial Areas in Surgery—17th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 18-21—**Basic Science for Surgeons.** STAN at The Lodge, Pebble Beach. Tuesday-Friday.

March 19-23—**Vascular Surgery—8th Annual Symposium.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 25-29—**3rd U.S. Intraocular Lens Symposium and 7th Scientific Session.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Tuesday-Saturday. 30 hrs. Contact: Debbi Miller, Dir. of Mtg. Services, AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 395-3937.

April 3-4—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 11-12—**New Techniques in Hip Resurfacing and Replacement: In-Depth Course and Workshop.** UCLA. Friday-Saturday.

April 18-19—**Workshop on Orthopedic Injuries.** PMC. Friday-Saturday.

April 19-20—**Office Orthopedics/Office Urology.** UCLA. Saturday-Sunday.

April 24-25—**11th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. Contact: Mrs. Lu Hendricks, JSEI, UCLA Sch. of Med., Los Angeles 90024.

April 24-26—**General Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday.

April 26-May 3—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

May 4—**Recent Advances in Surgery of the Lower Gastrointestinal Tract.** White Memorial Medical Center and LLU at Bonaventure Hotel, Los Angeles. Sunday. 8½ hrs. Contact: Dir., Cont. Med. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000.

May 9-10—**Combined Otolaryngologic/Orthognathic Symposium.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Friday-Saturday. 12 hrs. $195.

May 10—**Photocoagulation Therapy Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

May 15-17—**Nasal Plastic and Reconstructive Surgery.** PMC at Clift Hotel, San Francisco. Thursday-Saturday. 15 hrs. $250.

May 18-22—**American Urological Association.** Hilton, San Francisco. Sunday-Thursday. Contact: AUA, 1120 N. Charles St., Baltimore, MD 21201.

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May 29-30—**Neurosurgery Postgraduate Course.** UCSF at Hilton, San Francisco. Thursday-Friday.

May 29-31—**Oto '80.** Project HEAR at St. Francis Hotel, San Francisco. Thursday-Saturday. 24 hrs. $485. Contact: Judy Staton Thielke, Project HEAR, 1801 Page Mill Rd., Palo Alto 94304. (415) 494-2000.

OF INTEREST TO ALL PHYSICIANS

January 21-25—**Therapy: Principles and Use of Drugs.** STAN at Hyatt on Union Square, San Francisco. Monday-Friday. 25 hrs. $290.

January 23-25—**Sierra Traumatological Society—9th Annual Meeting.** Lodge, Bear Valley. Wednesday-Friday. Contact: Joseph B. Serra, MD, STS, P.O. Box 230, Stockton 95201. (209) 466-9535.

January 30-February 2—**Primary Care: Current Management of Common Office Problems.** UCSF. Wednesday-Friday.

January 31-February 2—**Medical and Legal Aspects of Asbestosis.** USC. Thursday-Saturday.

February 1-7—**LLU Alumni Association—48th Annual Postgraduate Convention.** One week.

February 2-3—**Conference on Human Sexuality: Working with Clients in the Gay Community.** UCLA at Airport Marina Hotel, Los Angeles. Saturday-Sunday. 12 hrs. $100.

February 4-9—**Family Practice Refresher Course—11th Annual.** UCI at Marriott Inn, Newport Beach. Monday-Saturday.

February 5-June 24—**Family Practice Review.** USC. Tuesday evenings.

February 7-9—**Obesity-Diabetes-Atherosclerosis Connection.** Eisenhower Medical Center at Gene Autry Hotel, Palm Springs. Thursday-Saturday. 12 hrs. $145. Contact: John Deller, MD, Dir. of Med. Ed., Eisenhower Med. Ctr., 39000 Bob Hope Dr., Rancho Mirage 92270. (714) 346-3911.

February 8-13—**California Medical Association—109th Annual Session.** Town and Country, San Diego. Friday-Wednesday. Contact: Rocki Lai, CMA.

February 9-10—**Sexual Therapy.** See Psychiatry, February 9-10.

February 10-13—**Medical Evaluation of the Preoperative Patient.** UCD at Hyatt Lake Tahoe, Incline Village. 15½ hrs. $135.

February 13—**Environmental Medicine.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 6 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Mosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 283.

February 13-15—**30th Annual Course for Physicians in Family Practice.** Mt. Zion Hosp. and Med. Ctr., San Francisco. Wednesday-Friday. 20 hrs. Contact: Heidi Benson, Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

February 14-15—**Management of the Ventilator Dependent Patient.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 14 hrs. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 15-16—**Health Care and the Changing Society.** Vista Hill Foundation and Mesa Vista Hosp. at Hotel del Coronado, Coronado. Friday-Saturday. 9 hrs. Contact: Virginia Everett, Vista Hill Foundation, 3420 Camino del Rio, Suite 100, San Diego 92108. (714) 563-1770.

February 21-22—**New and Old Antibiotics.** USC. Thursday-Friday.

February 21-23—**Musculoskeletal Diagnostics and Treatment—Towards a More Rational Perspective.** American Academy of Physical Medicine and Rehabilitation and Eisenhower Med. Ctr. at Gene Autry Hotel, Palm Springs. Thursday-Saturday. Contact: Paul H. Goodley, MD, Pain Diagnostics and Rehabilitation Institute, 2210 W. 3rd St., Los Angeles 90057. (213) 383-8485.

February 23-24—**Health in the Workplace.** UCSF Cont. Ed. Health Sciences. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

February 24-26—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Sunday-Tuesday. 21 hrs. $250.

February 25-29—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $290.

February 26-March 2—**Critical Care Medicine.** USC at Hilton, San Francisco. Tuesday-Sunday.

February 27—**Hospital Infection Control.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 7 hrs. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 27—**Drug Update—1980—18th Annual Symposium.** Eden Hospital, Castro Valley. Wednesday. Contact: Jay J. Protass, MD, Eden Hospital, 20103 Lake Chabot Rd., Castro Valley 94546. (415) 537-1235.

March 1—**New Frontiers in Clinical Medicine.** PMC. Saturday. 6 hrs. $85.

March 1-2—**Genetic Disorders.** UCLA. Saturday-Sunday.

March 5-April 23—**General Preventive Medicine.** USC. Wednesday evenings.

March 8-9—**Approaches to Healing—3rd Annual Course.** San Diego County Medical Society and UCSD at Town and Country Hotel, San Diego. Saturday-Sunday. 12 hrs. $150. Contact: Roger L. Youmans, MD, SDCMS, P.O. Box 23015, San Diego 92123.

March 8-9—**Clinical Hypnosis: Advanced Seminar.** San Diego and American Societies for Clinical Hypnosis, Education Research Fndn., Bay General Community Hosp. at Admiral Kidd Club, San Diego. Saturday-Sunday. 14 hrs. Contact: Errol R. Korn, MD, 480 4th Ave., Suite 409, Chula Vista 92010. (714) 420-8051.

March 9-15—**Critical Care II and Ski.** College of Medical Education, Pierce Co. (WA) Med. Soc. at Sahara Lake Tahoe, Incline Village. One week. Contact: Maxine Bailey, College of Med. Ed., Pierce Co. Med. Soc., 705 S. 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 9-16—**Sports Medicine.** Center for Sports Medicine, Northwestern Univ. Med. Sch.; Div. of Sports Med., No. Carolina Dept. of Public Instruction at Intercontinental Hotel, Maui, Hawaii. One week. Contact: Marianne Porter, Ctr. for Sports Med., 2-063, 303 E. Chicago Ave., Chicago 60611.

March 12—**Refresher in Family Practice.** N. T. Enloe Memorial Hosp. at Holiday Inn, Chico. Wednesday. 6 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 283.

March 15—**Medical Treatment of Alcoholism.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7 hrs.

March 15-16—**Practical ENT for Primary Care Physicians.** UCLA. Saturday-Sunday.

March 15-16—**Human Lymphocyte Antigens.** See Medicine, March 15-16.

March 15, 29—**The Placebo Effect: Optimizing the Therapeutic Power of the Doctor/Patient Relationship.** UCLA. Two Saturdays.

March 18-22—**Sports Medicine.** University of Hawaii School of Medicine at Princess Kaiulani Hotel, Waikiki, Honolulu, Hawaii. Tuesday-Saturday. 18 hrs. $200. Contact: Hawaii Conference Services, P.O. Box 25055, Honolulu 96825. (808) 377-6445.

March 19-21—**American Society for Clinical Pharmacology and Therapeutics.** Fairmont Hotel, San Francisco. Wednesday-Friday. Contact: E. H. Funk, Jr., MD, ASCPT, 1718 Gallagher Rd., Norristown, PA 19401.

March 20-23—**4th Annual Basic Clinical Hypnosis Workshop.** UCI at Balboa Bay Club, Newport Beach. Thursday-Sunday.

March 22-23—**Contraception: Current Research and Multidisciplinary Applications.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

March 24-28—**Postgraduate Institute for Primary Care Physicians.** UCSD at Vacation Village, San Diego. Monday-Friday.

March 31-April 2—**Football Injury Workshop.** Center for Sports Medicine, St. Francis Memorial Hospital at Jack Tar Hotel, San Francisco. Monday-Wednesday. $165. Contact: Ctr. for Sports Medicine, St. Francis Mem. Hosp., 900 Hyde St., San Francisco 94109. (415) 775-4321, ext. 3370.

April 7-9—**Clinical Dermatology for the Family Practitioner.** UCD at Ahwahnee Hotel, Yosemite. Monday-Wednesday. 20 hrs.

April 8, 15, 22, 29, May 3—**Therapeutic Movement, Manipulation and Massage.** UCLA. Tuesdays.

April 9-11—**Bacteriology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 20 hrs. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 9-12—**Nosocomial Infection.** Memorial Hospital Medical Center-UCI Center for Health Education. Wednesday-Saturday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 13-25—**Mental Retardation.** UCLA. Two weeks.

April 17-19—**Wound Management Workshop.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

April 21-25—**1980 Family Practice Review.** PMC at Claremont Hotel, Berkeley. Monday-Friday. 27 hrs. $350.

April 24-27—**Postgraduate Institute.** CMA and USC at Ahwahnee Hotel, Yosemite. Thursday-Sunday. Contact: Charlotte Newhart, CMA.

April 26-27—**Deafness: The Silent Barrier to Health Care.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

May 1-2—**Therapeutic Drug Monitoring.** PMC. Thursday-Friday. 12 hrs.

May 10, 24—**Clinical Nutrition.** UCLA. Two Saturdays.

May 12-15—**Aerospace Medical Association.** Disneyland Hotel, Anaheim. Monday-Thursday. Contact: R. R. Hessberg, MD, Washington Nat'l Airport, Washington, DC 20001.

May 13-19—**Basic Diving Medicine.** UCSF. One week.

May 14—**Deafness and Its Management.** LLU. Wednesday. 4 hrs. $30.

May 16-18—**2nd Annual National Symposium on Sexuality and Disability.** UCSF. Friday-Sunday. Contact: UCSF Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

May 18-23—**Fingers-to-the-Toes: An Orthopaedic Approach for the Family Practitioner.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Friday.

May 19-23—**7th Annual Family Practice Refresher Course.** UCLA and Santa Monica Hospital Medical Center at Sheraton-Miramar, Santa Monica. Monday-Friday. Contact: UCLA.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

SEMINARS IN FAMILY MEDICINE

Editor: L. ROBERT MARTIN, M.D.

Now—a new journal dedicated to the concept of the Family Physician as a specialist in a dynamic and complex field of medicine. Within a clear, readable format and with a uniformly high level of professionalism, the Editors present in each quarterly issue a concise and comprehensive treatment of a specific subject area vital to the practice of Family Medicine.

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VOLUME I
Number 1 (February 1980)
MANAGEMENT OF THE MYOCARDIAL INFARCTION
Number 2 (May 1980)
FINANCIAL MANAGEMENT OF THE OFFICE PRACTICE
Number 3 (August 1980)
PEPTIC DISEASE
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ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

February 7—**Diagnosis of Organic Brain Syndrome—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

March 20—**Treatment Outcome Study, Harborview Community Health Center—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

March 26—**Utilization of Midlevel Practitioners—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

May 1—**Child and Community Psychiatry—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

May 28—**Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday, 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

June 19—**Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

MONTANA

January 23-25—**Health Advice for Travelers; New Developments in Diagnosis and Therapy of Parasitic Disease—Univ. of Wash. Internal Medicine Review Sessions.**

January 23, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

January 24, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

January 25, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

February 13—**Pediatric Arthritis-Immunology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 20-22—**Diagnosis and Management of Bleeding Disorders—Univ. of Wash. Internal Medicine Review Sessions.**

February 20, Wednesday, Great Falls, 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 21, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

February 22, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

February 23-24—**Annual Mid-Winter Meeting, Montana Academy of Dermatology.** Big Sky. Saturday-Sunday. Huntley Lodge. Contact: John R. Tkach, MD, 300 N. Willson, Bozeman, MT 59715. (406) 587-5442.

February 29-March 1—**Annual Medical Seminar.** Big Sky. Friday-Saturday. Huntley Lodge. Contact: D. Frank Johnson, MD, Interhospital Continuing Medical Education Department, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 12—**Pediatric Hematology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 26-28—**The Eye and Internal Disease—Univ. of Wash. Internal Medicine Review Sessions.**

March 26, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 27, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

March 28, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 9—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 16-18—**Office Gynecology—Univ. of Wash. Internal Medicine Review Sessions.**

April 16, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 17, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

April 18, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

May 7—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28-30—**Nuclear Medicine for Internists—Univ. of Wash. Internal Medicine Review Sessions.**

May 28, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 29, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

May 30, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 52 West Pine, Missoula, MT 59801. (406) 549-3782.

June 11-13—**Transient Ischemic Attack and Stroke; Seizure Disorders—Univ. of Wash. Internal Medicine Review Sessions.**

June 11, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

June 12, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

June 13, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

IDAHO

January 22—**Pediatric Surgery—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

January 30-February 3—**Seminar in the Snow: A Postgraduate Course in Emergency Medicine.** Elkhorn Village, Sun Valley. Wednesday-Sunday. Contact D. Craig Dennis, MD, 897 MacArthur Blvd., San Leandro, CA 94577. (415) 632-1504.

February 9-16—**Sun Valley Critical Care: Maternal/Perinatal.** Sun Valley, Idaho. Saturday thru Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 23-March 1—**Office Orthopedics for Primary Physicians.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 26—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

March 1-8—**Current Concepts in Medicine—Good Samaritan Hospital, San Jose, California.** Sun Valley. Saturday-Saturday. Contact: Daman-Nelson Travel, 115 Mission St., San Francisco, CA 94105. (415) 982-3307.

March 8-15—**Psychiatry for Primary Physicians.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 15-22—**Sports Medicine.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 17—**Shock in Pregnancy—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

March 25—**Pediatric Arthritis and Immunology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

April 14—**Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

April 22—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

May 19—**Hypertension and Pregnancy—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 20—**Dysmorphology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony's Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 11-15—**Eleventh Annual Family Practice Review.** Portland, Monday-Friday. Hilton Hotel. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

February 10—**What's New in Perinatal Medicine—March of Dimes Birth Defects Foundation and The Oregon Academy of Family Physicians.** Portland, Sunday. Jantzen Beach, Red Lion Inn. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 17-20—**American College of Physicians Review Course.** Portland, Tuesday-Friday. Jantzen Beach Thunderbird. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 25-27—**Symposium on Sports Medicine.** Eugene, Wednesday-Friday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

January 17-18—**Pediatric Update.** Seattle. Thursday-Friday. Children's Orthopedic Hospital and Medical Center. Contact: W. O. Robertson, MD, COHMC: ZC-10, 4800 Sand Point Way NE, Seattle, WA 98105. (206) 634-5072.

January 23-February 1—**Critical Care I and Ski.** Val Gardenia, Italian Alps. Ten Days. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

January 25—**Current Urological Considerations.** Seattle. Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

January 26—**Useful Radiology in Primary Care—Part I: Above the Diaphragm.** Seattle. Saturday. Group Health, Sixth Floor Conference Facility. Contact: Jackie Taylor, Group Health Cooperative of Puget Sound, 201 16th Avenue E, No. 321, A-5, Seattle, WA 98112. (206) 326-7349.

January 26—**Rheumatology.** Tacoma. Saturday. St. Joseph Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

January 29-30—**Tax Estate and Financial Planning.** Seattle. Tuesday-Wednesday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

January 31, February 1-2—**Neuro-ophthalmology—Annual President's Meeting.** Seattle. Thursday-Saturday. Olympic Hotel. Contact: Marcia Wahlman, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Room 900, Seattle, WA 98121. (206) 623-4801.

February 1-2—**Violence in the Family.** Seattle. Friday-Saturday. Swedish Hospital Auditorium. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 5-8—**Ski and Learn.** Crystal Mountain, WA. Thursday-Friday. Contact: Carolyn M. Palmer, Washington Academy of Family Physicians, 3700 140th Ave., NE, Bellevue, WA 98005. (206) 883-8852.

February 8-9—**Workshops in Endocrinology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

February 9-16—**Sun Valley Critical Care: Maternal/Perinatal.** Sun Valley, Idaho. Saturday thru Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 12—**Pediatric Arthritis-Immunology—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

February 15—**Peripheral Vascular Disease.** Tacoma. Friday. Tacoma General Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

February 18—**Endocrinology Circuit Course.** Vancouver, WA. Monday (4 hours). St. Joseph Community Hospital. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 19—**Endocrinology Circuit Course.** Longview. Tuesday (4 hours). Monticello Medical Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 20—**Endocrinology Circuit Course.** Olympia. Wednesday (4 hours). Tyee Motor Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 21—**Endocrinology Circuit Course.** Bremerton. Thursday. Harrison Memorial Hospital. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 22—**Endocrinology Circuit Course.** Bellingham. Friday. Western Washington University. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 22-23—**Psychiatric Management of the Problem of Pain.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

February 23-March 1—**Office Orthopedics for Primary Physicians.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 25—**Renal Pathophysiology and Renal Failure—Univ. of Wash., Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

February 26—**Gyn Oncology—Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

February 28-29—**Northwest Stroke Symposium.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: Education and Training Department, Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

March 6-7—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 8-15—**Psychiatry for Primary Physicians.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 9-15—**Critical Care II and Ski.** Lake Tahoe, Nevada. Thursday-Wednesday. Sahara Tahoe. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 11—**Pediatric Hematology—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m. Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medicine Center, Spokane, WA 99204. (509) 455-8220.

March 13-14—**Tacoma Academy of Internal Medicine Annual Scientific Program.** Tacoma. Thursday-Friday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 14-15—**Pharmacology for the Practitioner.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

March 15-22—**Sports Medicine.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 17-28—**Rehabilitation Medicine Review.** Seattle. Two weeks. University Towers Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 18—**Shock in Pregnancy—Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

March 21-22—**Days of Pediatrics.** Tacoma. Friday-Saturday. Mary Bridge Children's Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98450. (206) 627-7137.

March 24—**Ischemic Heart Disease—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 24-28—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 29-April 5—**Infectious Diseases.** Hilo, Hawaii. Saturday-Saturday. Naniloa and Kona Surf Hotels. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 31-April 3—**American College of Physicians: Hematology.** Seattle. Monday-Thursday. Olympic Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 3-4—**Hazards to the Fetus.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 8—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

April 10-11—**Dermatology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 10-11—**Annual Cancer Symposium—Gastrointestinal.** Seattle. Thursday-Friday. Swedish Hospital and Medical Center. Contact: John L. Wright, MD, Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

April 12—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

April 15—**Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

April 17-18—**Couples.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 18-19—**Tacoma Surgical Society Annual Scientific Program.** Tacoma. Friday-Saturday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

April 24-25—**Respiratory Care.** Seattle. Thursday-Friday. Contract: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 24-25—**Review of Arrythmias.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 25-26—**Anesthesia: Low Flow States—Pathology and Treatment.** Vancouver, British Columbia. Friday-Saturday. Four Seasons Hotel. Contact: Dr. K. Turnbull, Academy of Medicine, 1807 West 10th Avenue, Vancouver, BC V6J 2A9.

April 28—**Cardiomyopathies and Pericardial Disease—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 1-2—**Controversies in Medicine.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 2-3—**Contemporary Clinical Neurology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 5-6—**Patient-Physician Relationship.** Port Ludlow. Monday-Tuesday. The Admiralty. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 6—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Spokane). 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

May 8-10—**Washington Academy of Family Physicians—Annual Scientific Assembly.** Seattle. Thursday-Saturday. Red Lion Inn/Seattle-Tacoma Airport. 14 prescribed hours. Contact: Carolyn M. Palmer, Washington Academy of Family Physicians, 3700 140th Ave., NE, Bellevue, WA 98005. (206) 883-8852.

May 12—**Principles of Antibiotic Therapy—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 16-17—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 20—**Hypertension and Pregnancy—Univ. of Wash. OB-GYN Sessions** (Spokane). 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 22-23—**Adolescent Medicine.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 30—**Ophthalmology in Family Practice.** Seattle. Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 6-7—**Workshops in Musculoskeletal Disease.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Renal Disease.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 19-20—**Laboratory Medicine.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 23—**Basic Concepts of Immunology and Their Application—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

June 26-27—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 28-July 5—**Alaska Cruise—Emergency Medical Care: Trauma, Orthopedics and Surgery; Biomedical History.** 8 days. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

January 18
SPONSOR: Hill Air Force Hospital
TITLE: **Everyday Common Skin Disease**
LOCATION: HAFB Hospital Phys. Exam. Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

January 23-26
SPONSOR: University of Utah
TITLE: **Immunology and Infections in Pregnancy**
LOCATION: Snowbird, Utah
FEE: $250
CREDIT: 16.5 hours
CONTACT: James Scott, MD (801) 581-7647

January 26-February 2
SPONSOR: University of Utah
TITLE: **Radiology of the Traumatized and Acutely Ill Patient**
LOCATION: Snowbird, Utah
FEE: $240
CREDIT: 20 hours
CONTACT: Rebecca Peay (801) 581-8118
(This is the first of two identical conferences)

January 30-February 2
SPONSOR: Intermountain Thoracic Society/Pacific Northwest Chapter—American College of Chest Physicians
TITLE: **23rd Annual Mid-Winter Conference on Chest Disease**
LOCATION: Snowbird, Utah
FEE: Members—$50
Non-members—$75
Allied Health Workers—$20
Students—no fee
CREDIT: 20 hours
CONTACT: Ted Bernhisel, MD (801) 364-5673

February 1
SPONSOR: Hill Air Force Base
TITLE: **Cardiac Arrythmia**
LOCATION: HAFB Hospital Phys. Exam. Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

February 8
SPONSOR: Hill Air Force Base
TITLE: **Hypertension in General Practice**
LOCATION: HAFB Hospital Phys. Exam. Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

February 8
SPONSOR: McKay-Dee Hospital/Arthritis Foundation
TITLE: **Arthritis Seminar**
LOCATION: McKay-Dee Hospital
FEE: $20 (students free)
CREDIT: 7 hours
CONTACT: Lucille Taylor (801) 399-4141 (Ext. 2251)

February 11-14
SPONSOR: University of Utah
TITLE: **9th Annual Family Practice Refresher Course**
LOCATION: Salt Lake Hilton
FEE: $225
CREDIT: 28 hours
CONTACT: John Tudor, Jr., MD (801) 581-8633

February 13-15
SPONSOR: University of Utah
TITLE: **Update of Clinical Microbiology and Immunology**
LOCATION: Holiday Inn, Park City, Utah
FEE: $190
CREDIT: 18 hours
CONTACT: John Matsen, MD (801) 581-5514

February 15
SPONSOR: Hill Air Force Hospital
TITLE: **Chest X-Rays with Cardiac Significance**
LOCATION: HAFB Hospital Phys. Exam. Room
FEE: None
CONTACT: Harold S. Jenson, MD (801) 777-3030

February 15-19
SPONSOR: University of Utah
TITLE: **The Heart and Peripheral Vascular System—25th Annual Postgraduate Course in Anesthesiology**
LOCATION: Hotel Utah, Salt Lake City
FEE: $200
CREDIT: 16 hours
CONTACT: Theodore Stanley, MD (801) 581-6393

February 21-23
SPONSOR: University of Utah
TITLE: **21st Annual Obstetrics and Gynecology Course**
LOCATION: Holiday Inn, Park City, Utah
FEE: $250
CREDIT: 16.5 hours
CONTACT: David Engleberg (801) 581-3087

SPONSORS OF LISTED COURSES—ABBREVIATIONS

AF	Arthritis Foundation
HAFB	Hill Air Force Base
LDSH	LDS Hospital
MDH	McKay-Dee Hospital
OEH	Center/Occupational & Environmental Health
PCMC	Primary Children's Medical Center
SLSC	Salt Lake Surgical Center
UAFP	Utah Association of Family Practice
UU	University of Utah
UVH	Utah Valley Hospital
VAH	Veteran's Administration Hospital
SHCC	Shriners Hospital for Crippled Children

February 24-March 1
SPONSOR: University of Utah
TITLE: **Radiology of the Traumatized and Acutely Ill Patient**
LOCATION: Park City, Utah
FEE: $240
CREDIT: 20 hours
CONTACT: Rebecca Peay (801) 581-8118

February 25-27
SPONSOR: University of Utah
TITLE: **Practical Pediatrics Review and Update**
LOCATION: Salt Lake Hilton
FEE: $150
CREDIT: 16 hours
CONTACT: Dennis Ashton, MD (801) 942-1800

February 28-March 1
SPONSOR: Salt Lake Surgical Center
TITLE: **6th Annual Meeting—Society for the Advancement of Free Standing Ambulatory Surgical Care**
LOCATION: Hotel Utah, Salt Lake City
FEE: Members—$170
Non-members—$195
Nurses—$95
CREDIT: 16 hours
CONTACT: Harry Wong, MD (801) 261-3141

February 29
SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology**
LOCATION: 7th Floor Conf. Room, LDS Hospital, Salt Lake City
FEE: $25
CREDIT: 3 hours
CONTACT: Stanley Everett (801) 350-1867

March 7-8
SPONSOR: UAFP
TITLE: **UAFP Annual Meeting**
LOCATION: Little America, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Janet Davis (801) 466-9478

March 8
SPONSOR: Hill Air Force Hospital
TITLE: **Emergency Procedures**
LOCATION: HAFB Hospital Phys. Exam. Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

March 12-14
SPONSOR: InterWest Regional Med. Ed. Center
VA Medical Center
TITLE: **Neurological Update for Physicians and Nurses**
FEE: To be announced
CREDIT: To be announced
CONTACT: Ida Bickle, RN (801) 582-1565 (Ext. 681)

March 14
SPONSOR: Hill Air Force Hospital
TITLE: **Common ER Surgical Procedures**
LOCATION: HAFB Hospital Phys. Exam. Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

March 17-21
SPONSOR: University of Utah
TITLE: **Advances in Internal Medicine Conference**
LOCATION: Snowbird, Utah
FEE: $200
CREDIT: 22.5 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

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WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-9, 1980, McKinley Village Lodge.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 23-27, 1980, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: February 8-13, 1980, Town and Country, San Diego.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 24-27, 1980, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: 1980—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1980, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 2-4, 1980, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 16-18, 1980, MGM Grand, Las Vegas.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 7-9, 1980, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-31, 1980, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 30-October 3, 1980, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 2-5, 1980, Thunderbird at Jantzen Beach, Vancouver, WA.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 23-27, 1980, Snow King Inn, Jackson.

March 21

SPONSOR: Shriners Hospital for Crippled Children
TITLE: **18th Annual Scientific Session**
LOCATION: Shriners Hospital, Salt Lake City
FEE: To be announced
CREDIT: 12 hours
CONTACT: Grace Miya (801) 532-5307

March 21

SPONSOR: Hill Air Force Hospital
TITLE: **Emergency Transportation Problems and Abdominal Trauma**
LOCATION: HAFB Hospital Phys. Exam. Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

March 24-28

SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird, Utah
FEE: $200
CREDIT: 22.5 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

March 27-29

SPONSOR: Rocky Mountain Center for Occupational and Environmental Health/Harvard School of Public Health
TITLE: **2nd Annual Park City Environmental Health Conference**
LOCATION: Park City, Utah
FEE: Pending
CREDIT: 20 hours
CONTACT: Katharine Blosch (801) 581-7182

March 29

SPONSOR: Utah Heart Association
TITLE: **Scientific Session**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Florence Christensen (801) 322-5601

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

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Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies, or with impaired renal or hepatic function. Periodic blood counts and liver and kidney function tests are advised during repeated therapy.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, e.g. excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
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REFERENCES:
1. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
2. Dement WC, *et al*: *Behav Med* 5:25-31, Oct 1978
3. Kales A, *et al*: *Clin Pharmacol Ther* 19:576-583, May 1976

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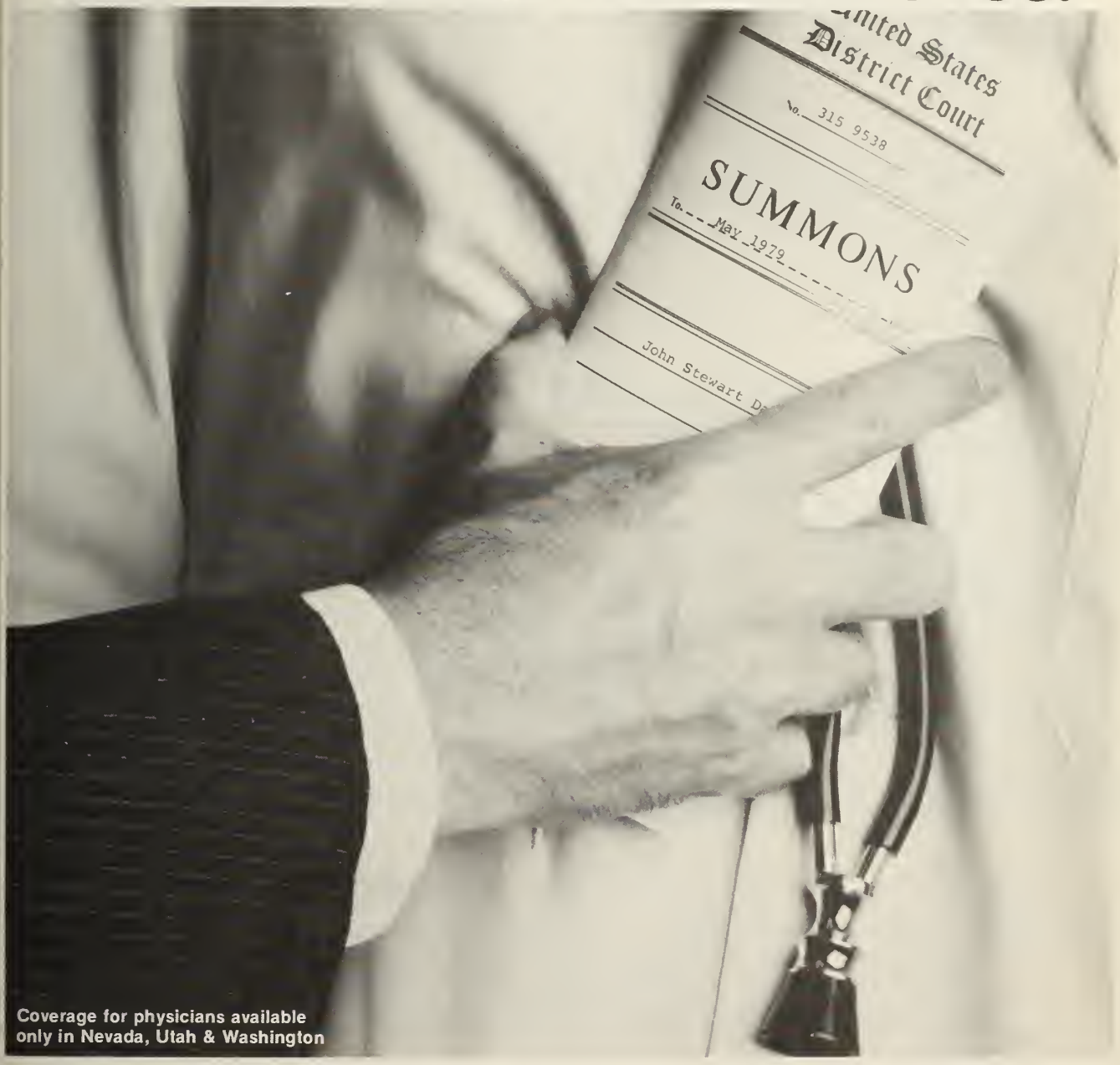

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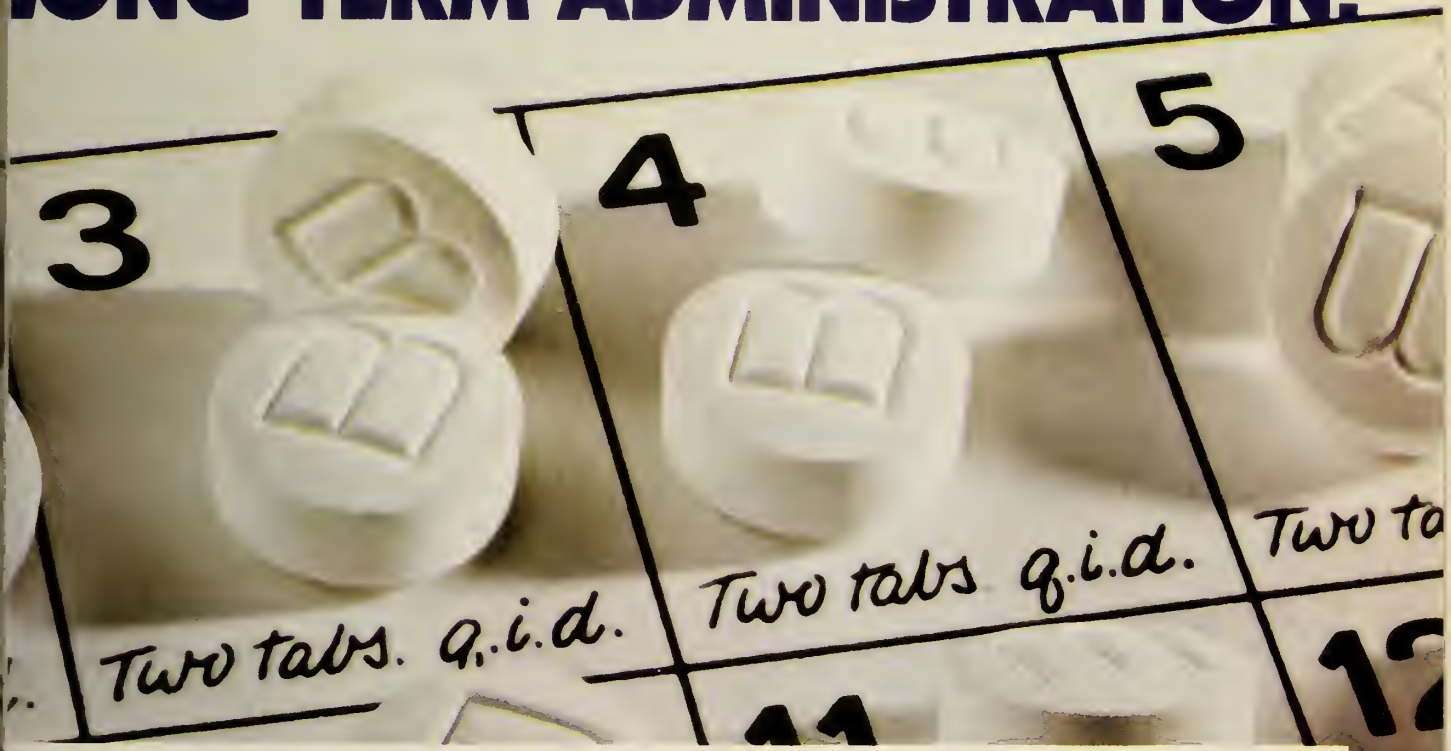

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SAN FRANCISCO BAY AREA—Two Top Level Positions. Alcohol, Drug Abuse and Mental Health Director. To manage a Multi-Service Division of the Health Services Department which includes alcohol, drug abuse and mental health program services. Responsibilities include preparation of the annual budget, program policy and planning, pursuit of funding sources, advising and consulting with program management and community advisory boards. Desired qualifications are: A psychiatrist, administrator, clinical or counseling psychologist, or Social Worker and six years of administrative and supervisory experience in a multi-service mental health organization. Salary is approximately $45,000-$55,000 plus fringe benefits. **Health Services Administrative Officer.** To direct the Management and Administration Division of the Health Services Department which contains centralized administrative activity that supports Public Health, Medical Care, and Alcohol, Drug Abuse and Mental Health program divisions. The appointee reports to the department Director and serves three major roles: Advise and consult with the Director and Program Division Managers regarding all aspects of department management and administration; monitor and evaluate the operations of the Department; and direct the day-to-day operations of the Management and Administration Division. Desired qualifications are Bachelors Degree in Public Administration, Business Administration or closely related health care field and six years of administrative or managerial experience in a health care organization which included significant participation in policy determination and operations. Salary: $35,484-$43,140 plus fringe benefits. Final filing date for both positions is March 21, 1980. Contact: Contra Costa County Personnel Department, 651 Pine Street, Martinez, CA 94553. Telephone (415) 372-4046. Equal Opportunity Employer.

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FACULTY POSITION—Department of Biological Chemistry, University of California, Davis, School of Medicine. Applications are invited for a faculty position at the rank of assistant or associate professor, to begin Spring or Summer 1980. Candidate should be active in research, capable of contributing significantly to Medical School and Graduate teaching in the areas of biochemistry, physiological chemistry, cellular and molecular biology. Quality and originality of research will receive greater emphasis than field of specialization although potential to enter into interdisciplinary research within the Department, encompassing the areas mentioned above will be given favorable consideration. Applicants should send a curriculum vitae, list of publications, future research plans and the names of at least three individuals from whom letters of recommendation may be solicited by the Search Committee to: Dr. Robert R. Traut, Chairperson, Search Committee, Department of Biological Chemistry, School of Medicine, University of California, Davis, CA 95616. Completed applications should be received not later than February 15, 1980. The University of California is an affirmative action/equal opportunity employer. Women and minority candidates are encouraged to apply.

INTERNIST—Board certified for active medical service, GM & S VA Medical Center in San Francisco Bay Area. CME encouraged. 30 days annual leave; 15 days sick leave: 9 paid holidays; inexpensive health & life insurance coverage available. Salary dependent upon experience and qualifications. Write or call John F. Kane, MD, Chief of Staff, VA Medical Center, Livermore, CA 94550. Phone (415) 447-2560, ext 204.

PHYSICIANS WANTED

WYOMING—Emergency physician needed to join three others in Cheyenne. ACLS certification necessary. Experience and ability to meet board credential requirements desirable. Unique organization, multiple hospital group owned by all the physicians. Profits returned to physicians, not to entrepreneur. Contact: American Medical Services Association, 4400 Broadway—Suite 306, Kansas City, Missouri 64111, (816) 931-3040.

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FP/GP needed in small, growing rural ambulatory health center. Provide and oversee pt. care, precept nurse practitioner. No admin. duties, call is negotiable, malpractice paid. Competitive salary, fringe benefits, good tax shelters. Local accred. hospital, good school system, base of Sierras—year-round recreation. Contact Peter Berger, Porterville Family Health Center, 1243 E. Date, Porterville, CA 93257. Tel. (209) 781-7242.

GENERAL PRACTITIONERS needed for Cut Bank, Montana and Green River, Wyoming. Must perform general medicine and participate in research projects. Salary $45,000-$50,000, malpractice, health insurance, pension, relief coverage for vacation and CME. Contact Comprehensive Health Systems, Office of the Medical Director, 2400 West 7800 South, Suite 202, West Jordan, Utah 84084. 1-800-453-6403.

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(Continued on Page 12)

(Continued from Page 11)

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BOARD CERTIFIED RADIOLOGIST, seeking a part or full time position in small community Hospital in Northern California or in the Valley. Solo or partnership. Curriculum Vitae and references at your request. Write Box 6070, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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GENERAL SURGEON, 36, board certified, experienced in general, thoracic and vascular. Also one year fellowship in Hand Surgery at top institutions. Solo or group practice preferred. Write Box 6091, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PODIATRIST, residency-trained, three years of military sxperience. Well versed in all phases of podiatry. Seeks to join multi-specialty group in Puget Sound Area, July, 1980. Contact HMR 1546, Keesler AFB, MS 39534.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

BARRON'S GUIDE TO FINANCIAL AID FOR MEDICAL STUDENTS—Dr. Stephen H. Lazar, Assistant Dean, Albert Einstein College of Medicine. Barron's Educational Series, Inc., 113 Crossways Park Drive, Woodbury, NY (11797), 1979. 264 pages, $5.95; School price, $4.76 (paperback).

CLINICAL PHARMACY AND THERAPEUTICS—Second Edition—Edited by Eric T. Herfindal, PharmD, Clinical Professor and Chairman, Division of Clinical Pharmacy, School of Pharmacy, University of California, San Francisco; and Joseph L. Hirschman, PharmD, Associate Clinical Professor, School of Pharmacy, University of California, San Francisco; General Manager, Professional Health Research, A Division of Health Systems Institute, Burlingame, California. Williams & Wilkins, 428 E. Preston Street, Baltimore, MD (21202), 1979. 719 pages, $29.95.

CONTINUOUS TRANSCUTANEOUS BLOOD GAS MONITORING: The National Foundation—March of Dimes Defects: Original Article Series, Volume XV, Number 4, 1979—Editors: Albert Huch, MD, Chairman and Professor, Department of Obstetrics, University of Zurich, Switzerland; Renate Huch, MD, Professor, Department of Obstetrics, University of Zurich; and Jerold F. Lucey, MD, Humboldt Senior Scientist Awardee, Professor of Pediatrics, University of Vermont, Burlington, VT. Alan R. Liss, Inc., 150 Fifth Ave., New York (10011), 1979. 638 pages, $68.00.

DEVELOPMENTAL ASPECTS OF CRANIOFACIAL DYSMORPHOLOGY: The National Foundation—March of Dimes Birth Defects: Original Article Series, Volume XV, Number 8, 1979—Editors: Michael Melnick, DDS, PhD,, Laboratory for Developmental Biology, Andrus Gerontology Center, University of Southern California, Los Angeles; and Ronald Jorgenson, DDS, Editor, Society of Craniofacial Genetics; Section of Clinical Genetics, Department of Oral Medicine, Medical University of South Carolina, Charleston; Associate Editor: Natalie W. Paul, The National Foundation. Alan R. Liss, Inc., 150 Fifth Ave., New York City (10011), 1979. 116 pages, no price given.

DRUG TREATMENT—Principles and Practice of Clinical Pharmacology and Therapeutics—Second Edition—Edited by Graeme S. Avery, Editor-in-Chief, Australasian Drug Information Services, Division of ADIS Press, Sydney & Auckland; Editor: **Clinical Pharmacokinetics** and **Current Therapeutics.** ADIS Press USA, Inc., Building 3, Brooklyn Navy Yard, Brooklyn, NY (11205), 1980. 1,382 pages, $33.50.

EARL MINDELL'S VITAMIN BIBLE—Earl Mindell, PharmB, RPh, Rawson, Wade, 630 Third Ave., New York, NY (10017), 1979. 292 pages, $12.95 (cloth); $6.95 (paperback).

EXTERNAL EAR MALFORMATIONS: EPIDEMIOLOGY, GENETICS, AND NATURAL HISTORY, In Birth Defects: Original Article Series, Volume XV, Number 9—Editors: Michael Melnick, DDS, PhD, Laboratory for Developmental Biology, Andrus Gerontology Center, University of Southern California, Los Angeles; and Ntinos C. Myrianthopoulos, PhD, Developmental Neurology Branch, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, MD; Associate Editor: Natalie W. Paul, The National Foundation-March of Dimes. Alan R. Liss, Inc., 150 Fifth Ave., New York, NY (10011), 1979. 138 pages, $18.00.

FAMILY PRACTICE: Foundation of Changing Health Care—John P. Geyman, MD, Professor and Chairman, Department of Family Medicine, University of Washington School of Medicine, Seattle. Appleton-Century-Crofts, 292 Madison Ave., New York City (10017), 1980. 543 pages, $28.50.

THE HERITAGE OF NUCLEAR MEDICINE—Edited by Marshall Brucer, MD, C. Craig Harris, MS, William J. MacIntyre, PhD, and George V. Taplin, MD; Book Coordinator, James A. Sorenson, PhD. Society of Nuclear Medicine, 475 Park Avenue South, New York City (10016), 1979. 167 pages, $14.50 plus $1.00 for postage and handling.

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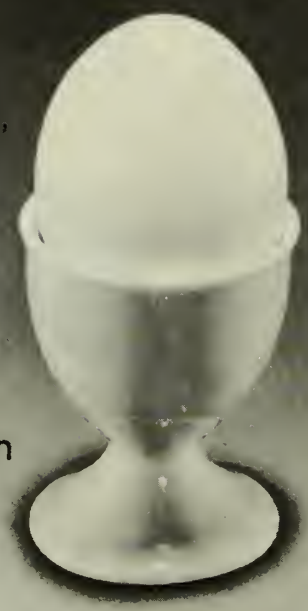

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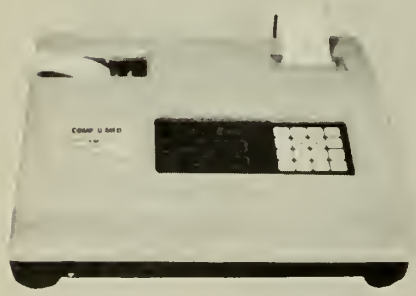

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Adverse Reactions to Radiographic Contrast Material

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Major adverse reactions to radiographic contrast media will occur more often as contrast material is now also administered during computerized tomographic (CT) scanning. Differentiation of the two major contrast reactions, the vagus reaction and the anaphylactoid reaction, is essential. Bradycardia is the key finding for identifying the vagus reaction. The vagus reaction involving hypotension and bradycardia requires treatment with large doses of atropine given intravenously. The immediate generalized reaction or anaphylactoid reaction should be treated as anaphylaxis with administration of vasopressors, fluids, steroids and antihistamines. Steroids and antihistamines given before the examination may offer protection to those high-risk patients who have had previous anaphylactoid reactions to contrast material.

THE USE of intravenously given radiographic contrast material is increasing. In addition to excretory urography, phlebography and angiography, radiographic contrast material is now frequently administered during computerized tomographic (CT) scanning of the head and body. Clinicians need to be aware of this practice because of its possible effects on patients who may have had previous reactions to the material. Treatment of these higher risk patients before repeat examinations has been advocated. The different types of adverse reactions need to be quickly recognized as well so that appropriate treatment can be initiated.

Of those patients receiving radiographic contrast material, up to 50 percent will have some type of untoward effect. Most of these will be mild, inconsequential vasomotor reactions. A mild or moderate immediate generalized reaction (IGR) or *anaphylactoid* reaction will develop in approximately 2 percent of patients. Severe reactions will occur in about one patient in a 1,000 and deaths in one in 40,000 of those receiving contrast material.[1-4]

Three types of adverse reactions have been recognized: (1) The vasomotor effect occurs in as many as 50 percent of patients receiving contrast material. It usually involves mild flushing, warmth, tingling sensations, a slight giddines, a metallic taste or perhaps nausea. This mild, transitory reaction is not life-threatening and is probably caused by the hypertonicity of the contrast material.[5-7] (2) The immediate generalized reaction (IGR), also termed the anaphylactoid reaction, designates the condition previously called the hypersensitivity reaction. However, it is not a true

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ABBREVIATIONS USED IN TEXT
CT = computerized tomography
IGR = immediate generalized reaction

anaphylactic reaction. The IGR may involve the development of urticaria, perhaps bronchospasm or laryngospasm, vasodilatation, hypotension and a compensatory tachycardia in patients.[8-11] The presence of tachycardia differentiates this type of reaction from the vagus reaction. (3) With the vagus reaction a patient becomes apprehensive, restless, gradually obtunded, sometimes loses sphincter control and may be apneic; hypotension and a profound bradycardia develop. Bradycardia is the key finding.[12] The differentiation of these latter two major reactions is very important and should determine appropriate treatment.

Discussion

Possible Mechanisms

There are few universally accepted facts about the mechanism of adverse reactions to radiographic contrast media. It appears that the anaphylactoid reaction relates to release of vasoactive and inflammatory agents by basophils and mast cells, and probably involves histamine.[5,9,13] The mechanism of release is uncertain but evidence suggests that a variety of mediators may be important. A direct effect by the contrast agent may occur in some cases;[14] components of the complement system have been implicated, particularly the anaphylatoxins C3a and C5a,[13,15] and a role by components of the coagulation system and prostaglandin inactivation has been suggested as well.[13,16] Although anaphylactoid reactions to contrast medium mimic IgE-mediated reactions, most evidence is against the contrast reaction being an immunologic reaction. Adverse reactions occur without previous exposure to contrast media and are not consistently reproducible, and attempts to show antibodies or circulating immune complexes have generally failed except in the study by Brasch.[3,4,7,9,17-19]

Although the series is small, the study by Simon, Schatz and associates, comparing patients exposed to radiographic contrast media without adverse reactions with those evidencing an anaphylactoid reaction showed no significant difference in the rise of plasma histamine, fall in complement level, presence of fibrin split products, personal history of allergy, previous exposure to contrast material or positive skin test to to contrast media.[17] Tissue responsiveness of each patient to mediators generated by several mechanisms may be the critical factor in adverse reactions to radiographic contrast material.[13]

Possible Risk Factors

Patients with allergies to foods or iodine, those with hayfever and, particularly, those with atopy show a higher incidence (up to 4 percent) of anaphylactoid reactions to contrast material than the expected 2 percent in the general population.[1,7,20] Of particular importance is the fact that patients who have had a previous IGR to contrast material show a much higher rate of reaction with a second administration of contrast medium—the rate increasing up to 35 percent.[10,11,18]

The frequency of major adverse reactions does not seem to increase with larger doses of contrast material[1] although the route of administration seems to affect the reaction rate. A larger number of reactions have been noted in patients after urograms (intravenous administration) were done than after arteriograms.[3] However, equally severe reactions have been observed[21] in the same patient when contrast material was given subcutaneously, intravenously and intraarterially. Small but definite intravascular levels of contrast medium can also be measured when retrograde pyelography or cystography is done. Therefore, even these examinations are not entirely innocuous in high-risk patients.[18]

Pretesting for the IGR or anaphylactoid reaction is not reproducible and is not recommended.[1,22,23] The value of graded intravenous pretesting has not been confirmed.

Vagus Reaction

The vagus reaction is a special type of reaction and is the one most likely to occur in patients after proctoscopy, cholangiography (intravenous administration) and common duct manipulation. The vagus reaction also probably accounts, in part, for the "caine" reaction or so-called hypersensitivity to local anesthetics. A profound vagus discharge may be elicited by the needle puncture, and it is this reaction that may be related to the fear-anxiety type reaction discussed by Lalli.[24] He strongly believes that the fear component plays a primary role in patients and their "allergic" reactions to contrast material.

The vagus reaction differs from the anaphy-

lactoid reaction in that hypotension and a profound bradycardia occur. Recognizing the bradycardia is critical because treatment of the vagus reaction involves giving the patient atropine and, perhaps, fluids intravenously. Antihistamines have very little effect on the vagus reaction. The vagus excess found with the vagus reaction causes vasodilatation, primarily in the postarteriolar phase, with venous pooling, lack of venous return and hypotension. Simultaneously, there is a depression of sinoatrial node activity causing bradycardia and arrhythmias.[25] Thus, instead of the expected tachycardia in response to the vasodilatation, a profound bradycardia occurs which, in turn, accentuates the hypotension.

Treatment of the vagus reaction requires aggressive intravenous administration of atropine.[8,12,26] Some feel that treatment with low doses of atropine is more life-threatening than helpful, and that it initially depresses sinoatrial node activity and increases arrhythmias; it is only with higher doses that this initial adverse reaction is reversed.[12] Treatment should begin with 0.6 to 0.8 mg of atropine given intravenously, followed by repeated doses every minute (while monitoring pulse rate) until a maximum total dosage of atropine (3 mg for adults) is administered. Fluids should then be given intravenously as well. The pulse rate is the most sensitive indicator of a patient's response to atropine because blood pressure may remain low for two to four hours despite adequate atropine treatment. However, by monitoring the pulse rate and administering large doses of atropine, the patient should respond clinically rather dramatically and show a reversal of apprehension, restlessness and depressed sensorium. Skin color may improve and pulse rate progressively increase. Routine pretreatment against the vagus reaction is not suggested for excretory urography because of the inability to predict in which patients a vagus reaction might develop. However, for angiography it may be worthwhile to treat highly anxious patients beforehand with intramuscular administration of 0.8 to 1 mg of atropine.

Anaphylactoid Reaction

Treatment for the immediate generalized reaction (anaphylactoid reaction) includes administration of vasopressors, fluids (intravenously), oxygen and, perhaps, antihistamines or steroids. Antihistamines are much less helpful once the reaction has fully developed although they probably neutralize circulating unbound histamine. Aminophylline is helpful for bronchospasm even though the aminophylline can accentuate any existing hypotension. Steroids are often empirically used, and most authors suggest giving high doses of corticosteroids intravenously when treating a severe immediate generalized reaction.[9,11,18,27]

Pretreatment or premedication for the anaphylactoid type reaction is now being advocated.[10,11,28] Both the Schatz group and the Zweiman group found it impossible to justify developing a control series of patients who previously had reacted to contrast material. In evaluating the contrast-reactive patients who were treated before the repeat examination (one group with antihistamines only, the other group with steroids only) and those who were not, the authors found that instead of an expected rate of 35 percent repeat contrast reaction there was a lower rate of 9 per-percent to 12 percent.[10,11] Without controls the significance of this finding can be argued. However, Kelly and associates report a recent prospective study that suggests that pretreatment offers protection against serious systemic reactions for high-risk patients who previously had experienced IGR.[28]

For those patients at high risk of having an anaphylactoid reaction, treatment with a combination of steroids and antihistamines is advocated using the following schedule.[28,29] Beginning 18 to 24 hours before the examination give 50 mg of prednisone orally every six to eight hours for three doses. Then give an antihistamine (such as Benadryl, 50 mg) orally or intramuscularly an hour before the examination. This recommended pretreatment with prednisone can be terminated without problem.

When a patient says, "I am allergic to x-ray dye" it is important to determine the type of adverse reaction that had actually occurred previously. If a patient had nausea, felt a tingling sensation or felt "flushed" after injection of the contrast medium, then a benign vasomotor effect had occurred. This reaction can be disregarded and does not need pretreatment or premedication. Conversely, if a patient had prominent hives, angioedema, bronchoconstriction or a hypotensive reaction, an IGR or anaphylactoid type reaction had occurred. It is suggested that these patients be treated with a combination of steroids and antihistamines before any further similar radiographic contrast material is administered. If a patient experienced hypotension and bradycar-

dia indicating a vagus reaction then administration of atropine before the test may be helpful. It is extremely important in patients with a serious history of previous contrast reactions that physicians review the indications for repeating the procedure and consider alternative diagnostic modalities such as ultrasonography, radionuclide imaging or CT scanning without use of contrast material.

Summary

Three types of adverse reactions to contrast media occur, the exact mechanisms of which are unknown. The vasomotor effect is usually not clinically significant. The immediate generalized reaction or anaphylactoid reaction varies in severity and is potentially life-threatening as is the vagus reaction. The anaphylactoid reaction should be managed like anaphylaxis with administration of fluids and vasopressors. Conversely, profound bradycardia in combination with hypotension identifies the vagus reaction and differentiates it from the IGR. Large doses of atropine given intravenously are specifically indicated for the vagus reaction. It is important to characterize the type of previous reactions, identify high-risk patients, and review the indications for any repeat examination. For those patients who have had a significant previous anaphylactoid reaction, treatment with a combination of steroids and antihistamines before the test is suggested.

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Gunshot Wounds to the Brain—A Civilian Experience

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A study involving 79 patients who were considered for surgical treatment for craniocerebral gunshot injuries between 1972 and 1978 was carried out to develop criteria for radiographic assessment and surgical operation, as well as to improve operative techniques and preoperative planning. The study focused on differences between military and civilian injuries, as well as criteria for gross prediction of outcome.

Of note in the overall perspective of the series were (1) the predominance of low-velocity missiles, (2) the high rate of self-inflicted injuries (34 percent), (3) the overall mortality of 23 percent with the rate for persons older than 60 being approximately 70 percent, (4) the correlation between preoperative patient assessment and mortality, (5) complications predominated by cerebrospinal fluid fistulas (10 percent), (6) the value of computerized axial tomographic (CAT) scanning in patient assessment and operative strategy and (7) the ultimate employability rate in survivors (78 percent).

An historical review of the development of management principles based on operative experience in the military sector as well as other recent civilian literature also deserves consideration.

CHANGES IN SOCIAL BEHAVIOR and attitudes are reflected in the diseases and injuries that medical practitioners confront in their patients. In the United States, assaults and deaths by firearms have increased substantially.[1,2] In one representative metropolitan county in the Midwest, the death rate attributed to such assaults increased 135 percent from 1960 to 1970.[2] This paper presents the experience of the Los Angeles County-University of Southern California (LAC-USC) Medical Center in treating gunshot wounds to the brain.

Management of this injury has been well documented in military experience.[3-27] The surgical principles of removal of foreign bodies and devitalized tissue, reduction of mass affect and the concepts of wound closure have not changed, but differences between military and civilian cases make analysis of gunshot wounds to the brain of timely interest.

Patients

The LAC-USC Medical Center is the primary trauma center for the southeastern region of the Los Angeles County which has a population of

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TABLE 1.—*Age Distribution of Patients*

Age (Years)	*Number of Cases (Percent)*
1-10	2 (2.5)
11-20	14 (17.7)
21-40	47 (59.5)
41-60	10 (12.7)
>60	6 (7.6)
TOTALS	79 (100.0)

TABLE 2.—*Mortality Versus Clinical Stage*

*Clinical Stage**	*Number of Patients (Percent)*	*Deaths (Percent)*
1	21 (27)	0 (0)
2	15 (19)	0 (0)
3	16 (20)	3 (19)
4	12 (15)	5 (42)
5	15 (19)	10 (67)
TOTALS	79 (100)	18 (23)

*Distribution of patients in each stage according to the seriousness of their condition before operation.

2.7 million and is the secondary referral center for the entire county, serving a population in excess of 8 million. The periods reviewed were from January 1972 to December 1976 and from January through December 1978. In the first period only patients undergoing surgical operations (N=65) were studied. During the second period, the review included all patients (N=34) with computerized axial tomographic (CAT) scanning data to rule out intracranial penetration from missile or bone fragmentation, or both. All charts were evaluated in a retrospective manner.

Of the patients in both periods who were treated surgically there were 64 males and 15 females. Ages ranged from 15 months to 81 years with a median of 21 years (Table 1). Most injuries resulted from low-muzzle energy weapons of .22 or .38 calibre. A single case was from a metal fragment of an exploding rifle.

Of the injuries, 34 percent were stated to be self-inflicted; 51 percent were entrance wounds between the nose and the right ear and 68 percent were entrance wounds on the right. These data are relevant when considering the final outcome and possible complications of this type of injury. The time from injury to admission to hospital ranged from ten minutes to three days, with a median of two hours. The time from injury to surgical operation ranged from two hours to 11 days with a median of ten hours.

The clinical rating system of Raimondi and Samuelson[25] was used. This system consists of five clinical grades:

- Stage 1—Alert, no loss of consciousness, no neurologic deficit;
- Stage 2—Alert, no loss of consciousness, localizing neurologic deficit;
- Stage 3—Awake, agitated, confused and lethargic;
- Stage 4—Comatose, responding only to pain;
- Stage 5—Comatose and posturing.

The distribution of patients in each stage was as follows: 21, stage 1; 15, stage 2; 16, stage 3; 12, stage 4, and 15, stage 5 (Table 2).

Management of Patients

All patients in coma were intubated to maintain adequate ventilation and to prevent aspiration. Arterial blood gases were monitored to insure adequate oxygenation and hyperventilation maintaining the carbon dioxide pressure (Pco_2) in the range of 25 to 30 mm of mercury. Intracranial monitors were used infrequently in the second review period. Antibiotics were given to 95 percent of the patients. Seventy-five percent received ampicillin alone in a dosage of 160 mg per kg of body weight per 24 hours in divided doses, initially administered intravenously and subsequently orally. Twenty percent received a second antibiotic (erythromycin, streptomycin, cephalothin sodium, kanamycin, methicillin or gentamicin), in conjunction with or after ampicillin for bacteriologically resistant infections. Diphenylhydantoin was used as the only anticonvulsant in 60 percent of the patients, 30 percent received both diphenylhydantoin and phenobarbital and 10 percent received no anticonvulsants.

Radiographic Assessment

Plain film findings were significant in that in 49 percent of the patients metal and bone fragments were noted only adjacent to the entrance site. Another 40 percent of the patients had metal or bone fragments, or both, at least 4 cm from the entrance site. In three patients, pneumocephalus was noted.

Cerebral angiography was done in 52 percent of the patients in the first review period. The decision for angiography was made on clinical and radiographic grounds. Clinical indications for angiography included a comatose status with preservation of brain stem reflexes and spon-

taneous respirations. The radiographic criterion for angiography was a 4-cm or greater separation between the entrance and exit wound or between the main missile mass and the entrance wound. Abnormal angiographic findings were identified in 31 of the 34 angiograms as follows: venous sinus occlusion, 5; traumatic aneurysm, 4; subdural hematoma, 11; epidural hematoma, 3; mass affect alone, 10, and mass affect and other lesions, 21.

In the second review period (1978) CAT scans were carried out on 34 patients who received gunshot wounds to the face or head. Studies were obtained in any neurologically viable person in whom intracranial penetration or injury was suspected. Ten showed no intracranial penetration. Of the remaining 24 patients, ten had no operation, seven because they were moribund at admission and three because there was felt to be no dural penetration. Of the 14 patients operated on, CAT scans showed the location of metal and bone fragments as well as the presence of intracerebral hematomas, contusions, depressed skull fractures or a combination of these complications.

Surgical Management and Findings

Patients selected for surgical treatment included all who could speak or follow simple commands and comatose patients who maintained respirations and brain stem reflexes. Apneic patients with no brain reflexes were not considered for operations. Procedures were designed to remove foreign material (such as metal and bone fragments, dirt, hair, powder granules), to evacuate extraaxial and intraaxial hematomas, to debride necrotic brain and soft tissue, and to achieve an adequate closure of the dura and soft tissue layers. The goals were to mitigate intracranial pressure excursions, to prevent infection and to establish a climate for maximum neurologic recovery.

Surgical findings (Table 3) established the presence of intracranial hematomas greater than 20 ml in volume in 52 percent of the patients. Essentially all cases had areas of nonviable contused cerebral tissue and 75 percent of the patients required a significant lobe resection. The entire missile tract was not routinely debrided. Bone fragments were removed only if they were within the field of resection or palpable immediately beneath this area. Deeper fragments were not pursued. Cultures of the wound and bone fragments were done. Dural closure was obtained in 80 percent of the cases. Irrigation with bacitracin was used throughout the surgical procedures. Skin closure consisted of a single layer of wire.

TABLE 3.—*Incidence of Intracranial Hematomas*

Type of Intracranial Hematoma	*Number of Cases* (Percent)*	*Percentage of Cases From Literature†*
Subdural hematoma	7 (9)	21
Intracerebral hematoma	21 (27)	23
Epidural hematoma	1 (1)	3
Subdural hematoma and/or epidural hematoma and/or intracerebral hematomas	12 (15)	..
TOTALS	41 (52)	47

*Total number of cases in study was 79.
†Byrnes, et al.[4]

TABLE 4.—*Mortality Versus Age*

Age of Patient (Years)	*Number of Patients*	*Deaths (Percent)*
1-10	2	0 (0)
11-20	14	5 (36)
21-40	47	7 (15)
41-60	10	2 (20)
> 60	6	4 (67)
TOTALS	79	18 (23)

Results

The overall mortality was 23 percent (Table 4). There were no deaths in stages 1 or 2 (Table 2). Mortality in stages 3, 4 and 5 were 19 percent, 42 percent and 67 percent, respectively (Table 2). There were five survivors in stage 5; two of these were able to care for themselves but unemployable, and three were dependent on others because of residual intellectual or physical deficits, or both. Mortality in patients older than 60 was 70 percent while for those in the 21 to 40 age group, mortality was 15 percent (Table 4).

Complications (Table 5) were dominated by cerebrospinal fluid (CSF) fistulas and seizures. There were eight patients with cerebrospinal fluid fistulas (seven rhinorrhea and one otorrhea). Meningitis developed in two of these patients despite administration of antibiotics. In five of the eight patients, fistulas resolved with nonsurgical management, in two surgical closure was required and one died with a persistent fistula. The high incidence of rhinorrhea reflects the frequency of close-range, basifrontal injuries.

Seizures were seen within the first week of injury in seven patients; in the four who survived, convulsive symptoms continued to occur. Late

TABLE 5.—*Complications Resulting From Gunshot Injuries*

		Patients
Disseminated intravascular coagulopathy		3
Obstructive hydrocephalus		1
Retained bone fragments		1
Postoperative cerebrospinal fluid fistulas		8*
Rhinorrhea	7	
Otorrhea	7	
Wound infections		5
Meningitis	4	
Cerebritis	1	
Seizures		21
Early	7	
Late	14	

*In five of the patients fistulas resolved without surgical treatment and in two surgical closure was needed. One patient died with a persistent fistula.

seizures—those observed a week or more after injury—were seen in 14 patients. The rate of incidence of seizures in cases followed for more than two years was 36 percent (18 of 50 survivors). Twenty of the 21 patients with early or late seizures began receiving anticonvulsants shortly after admission.

A second operative procedure was carried out in eight patients. The causes were persistent CSF fistulas in two patients, retained bone and metal fragments in two, subdural hygroma in one, wound infection in two and increased intracranial pressure in one. All three patients with diffuse intravascular coagulopathy died.

The follow-up of survivors is presented for the 1972 to 1976 series only, and ranged in length from six months to four years with a median of 27 months. Of the survivors, 78 percent were neurologically capable of employment; 8 percent were unemployable but self-sufficient and 14 percent remained dependent.

Discussion

Literature on missile wounds to the brain reflects primarily wartime experience.[3-21,23-27] Although there have been several civilian reports[1,4,9-11,25,28] published recently, the principles developed by military surgeons continue to provide basic guidelines.

The modern era of military neurosurgery began during World War I. Jefferson's review[17] stressed the importance of early operation to prevent sepsis and fungus cerebri. He felt fungus represented an increase in intracranial pressure secondary to sepsis and stressed the removal of the bone fragments driven into the brain. Cushing[12] introduced techniques of debridement and closure of open wounds.

In World War II the basic techniques of Cushing were used, although incisions had evolved from a tripod to a linear or curved configuration.[27] Local anesthesia was still preferred.[16] Although some[16,27] recommended a 48- to 72-hour delay in surgical procedures to allow stabilization, most surgeons advocated early operation.[20,21] Debridement of "macerated, devitalized cerebral tissue"[27] as well as foreign materials, bone fragments and clotted blood was stressed. The dura was opened under depressed skull fractures or open wounds if the dura appeared abnormal, whereas this was not done in World War I. Tight closure of the dura and skin were again recommended. Antibiotics were administered—penicillin (20,000 units given intramuscularly every three hours) and sulfadiazine being the only agents available.[27,29]

By the Korean war, the basic principles of early operation, debridement of bone and metal fragments, resection of devitalized tissue, closure of dura and skin, and prophylactic antibiotics were well established.[2,18,21,26] The importance of maintaining an adequate airway was recognized, and patients were nursed in the "coma" position or had tracheostomies.[21] A high incidence of intracranial hematomas was observed.[3,21] The necessity of a second surgical operation for removal of retained bone fragments was emphasized, although it was recognized that not all fragments could be removed because of their locations.[20]

In a Korean series,[3] 39 percent of missile wounds to the head were examined within three hours, 78 percent within six hours, and 88 percent within 8 hours. In Vietnam, patients were triaged by paramedical personnel while being transported by air to neurosurgical units.[19] One report stated that the average time from injury to admission and from admission to surgery was 45 minutes and 16 minutes, respectively.[19] Other series reported intervals of half an hour to five hours, and one to seven hours from injury to admission and from admission to surgery, respectively.[23] The choice of antibiotics available had changed. Chloramphenicol, penicillin, streptomycin and ampicillin were the drugs most frequently used.[19,23] Specialized power equipment, such as air-driven perforators, craniotomes and modern electrocautery units were available.[19,24] General anesthetics were used.[19,24] There was no hesitation

in opening the dura under depressed fractures if there were clinical signs of cortical damage or dural discoloration.[24]

A notable difference between gunshot wounds to the brain seen in warfare and those seen in civilian practice is due to the wounding agent. In Vietnam, only 20 percent to 38 percent of brain wounds were due to bullets.[19,24] Most missile wounds resulted from exploding metal fragments from high-velocity weapons, such as the American M-16 and the Russian AK-47 rifles, with muzzle velocities of 3,350 and 2,508 feet per second, respectively. The muzzle velocity of a hand gun is within 600 to 800 feet per second.[12] The energy imparted by a bullet is proportional to the mass times the square of the velocity, that is, $KE = 1/2\ mv^2$. The injuries in our series were remarkable in that 34 percent were self-inflicted, close-range and right-frontal. A total of 51 percent of the wounds were in the right frontal region. In the military, there was also a preponderance of frontal wounds,[24] but these were not reported as being basifrontal as was frequently seen in our injuries. This fact may be the reason why cerebral spinal fluid fistulas were much more frequent in our series (12 percent) than in the military (0.79 percent).[24] Our experience did not reflect any tangential wounds to the head with the massive brain guttering and soft tissue loss as described in the military literature.

This clinical series does not describe the management of patients dying without surgical operations. Of the patients with gunshot wounds of the brain admitted to our center, 30 percent died with no operation. In a Vietnam series of 2,187 cases of missile wounds to the head, 20 percent died without surgical operation.[14] These figures are not comparable because of differences and reasons already stated between military and civilian wounds, but they make the point that a significant number of patients do not survive long enough for surgical treatment. The criterion for selection of patients for surgical procedures is a predominant variable influencing overall outcome. In one Vietnam series,[19] the authors stated that "those with bilateral nonreactive pupils, general extremis, rigidity and Cheyne-Stokes respiration" were accorded the lowest surgical priority. Authors of a second study[23] stated inoperability of injuries of the head was indicated by a progressive clinical deterioration in association with at least three of the four following observations: (1) coma, (2) serious central respiratory dysfunction, (3) absence of pupillary responses and (4) decorticate posturing.

TABLE 6.—*Mortality Associated With Surgical Treatment in Wartime Conflicts*

Author	*Percentage of Mortality*	*Conflict*
Jefferson[17]	19.3	World War I
Cushing[12]	28.3	World War I
Haynes[16]	13.0	World War II
Weaver[27]	12.3	World War II
Meirowsky[21]	7.8	Korea
Plaut[23]	11.9	Vietnam
Hammond[14]	9.7	Vietnam
Adeloye[31]	14.0	Nigeria
Byrnes[4]	56.0	Ireland

Operative mortality has shown a steady decline from World War I to the Vietnam conflict (Table 6).[30-32] Findings reported in a recent study from Belfast[5] are substantially out of line with those of other studies and deserve mention. The operative mortality was 56 percent. This figure is attributable to unique circumstances. The Royal Victorian Hospital is closely situated to the area of conflict. A medical officer was sent with each ambulance to retrieve the victims, who were brought directly to the hospital, usually within half an hour of wounding. If a patient was comatose or coughing and retching, he was intubated and placed under general anesthesia with controlled hyperventilation. Surgical procedures were carried out as soon as blood was available. It was considered that patients would have succumbed if not operated on with immediacy. The initiation of general anesthesia made evaluation and recognition of neurologic deterioration impossible. Therefore, surgeons were operating on patients who would not have been considered surgical candidates in other circumstances.

In the 1978 series, 10 of the 14 patients who were treated surgically were transferred to LAC-USC Medical Center from outside hospitals. Of the ten transferred patients, three either had neurologic deterioration documented from the time of their admission to the outside hospital to the time of their transfer to LAC-USC Medical Center or had neurologic deterioration documented shortly after their arrival at our medical center.

The differences in operative mortality in our series (23 percent) and in the Vietnam conflict (9 percent to 12 percent)[14,15,23,24] also reflect the ages of injured patients. In the age group of 21 to 40 years, mortality was 15 percent in our study.

The relationship of wound infection and re-

tained bone fragments has been controversial. The overall infection rate in World War I was so high, it is not comparable. In World War II, one series[29,33] reported an overall incidence rate of "deep infection" (such as cerebritis or abscess) of 16 percent. When this figure was divided between deep infections with bone fragments and deep infections without bone fragments, the infection rates were 40 percent and 4 percent, respectively. Another study of cases from World War II[34] reported an incidence rate of deep infections associated with retained bone fragments of 25 percent. Even in World War II some authors[34] felt that reexploration should be reserved for those with clusters of bone fragments, not those with single isolated bone fragments distant to the site of operation. In Vietnam, it was the Army command policy[5,19] that all retained bone fragments be removed in a subsequent surgical operation. The overall infection rate in Vietnam was variously reported as 12 percent, 14 percent and 15 percent, which was similar to that during World War II. However, the deaths directly attributed to infection represent only 2 percent of surgical cases.[5] The incidence of infection with retained fragments is difficult to evaluate because it was routine to reexplore postsurgical patients if fragments were found. One study from Vietnam[6,7] attempted to assess the infective potential of bone fragments—45 consecutive cases had cultures taken of the external wound, brain tissue and bone fragments. (The bone fragments, usually numbering seven to nine, were cultured together so that the infected potential of a single fragment could not be stated.) In the series of cultures obtained, 44 of 45 external wound cultures, 5 of 45 brain tissue cultures and 21 of 45 bone fragment cultures showed contamination. In that study bone fragments removed during a second operation in ten patients were cultured; of these, four yielded positive cultures. The authors reported that of 16 patients operated on a second time to remove retained fragments, four had serious complications (increased dysphasia, coma and epidural abcess) or died. The authors concluded that bone fragments should be removed only if they are readily accessible within the operative field. This is the approach used at the LAC-USC Medical Center. Repetition of surgical procedures for removal of retained bone fragments is rare.

Findings in our study were similar to those recorded in wartime experience regarding frequency and location of intracranial hematomas (Table 5).[3,33] The significance of these hematomas is that their localization determines appropriate surgical procedures. Matson[33] stated that if he saw a foreign body on the contralateral side from the entrance wound, he explored that side looking for hematomas. Another author[14] felt that after initial debridement at the entrance site, if the "walls of the debridement tract" did not collapse, oftentimes he carried out trephination of the contralateral hemisphere.

Another difference between civilian practice and military practice is the diagnostic modalities available. From Cushing's time to the Vietnam conflict, neurosurgeons were forced to rely on their clinical examinations and the plain radiographs. In our study, angiography was used exclusively during the 1972 to 1976 period and computerized axial tomographic scanning was used in 1978. CAT scanning has now replaced angiography except in unusual cases where a sinus or vascular injury is considered likely. Computerized tomographic scans have proved to be extremely useful in excluding intracranial penetration. CAT scanning accurately discloses the location of metal and bone fragments as well as hematomas, depressed fractures, and areas of contused and edematous brain tissue. Often it is possible to see the course of the bullet tract through the brain and to see points of ricochet within the cranium. Artifacts produced by the metal fragments have not decreased the usefulness of CAT scanning.

Conclusion

Our study reemphasizes the basic tenets of surgical care developed by wartime surgeons, and also suggests modifications in current civilian practice that can improve the care of gunshot victims. Evacuation systems should be organized as they were in Vietnam to bring patients from the scene of the injury to definitive care hospitals. CAT scanning provides a valuable radiographic adjunct, which facilitates and increases the accuracy and sophistication of operative planning. The question of repeated surgical procedures for retained bone fragments is still an unanswered one, although there is a rationale for not removing all retained bone fragments. The use of intracranial pressure monitoring may prove to be another area of improvement in treating victims of gunshot wounds to the brain.

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Magnesium Deficiency: An Unrecognized Cause of Convulsions, Arrhythmias, and Neuromuscular Impairment

TREATMENT OF HYPOCALCEMIA due to magnesium deficiency involves simply replacing the magnesium. It does little good to try to give large doses of vitamin D or calcium . . . . Although the serum magnesium level can go back up fairly promptly, it takes a number of days for a full effect of the magnesium to be manifested. So . . . we usually persist for at least five days.

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Refer to: Krouse HA, Santiago SM, Klaustermeyer WB: Intravenously given methylprednisolone in refractory asthma. West J Med 132:106-110, Feb 1980

Intravenously Given Methylprednisolone in Refractory Asthma

H. ALAN KROUSE, MD, *Seattle,* and SILVERIO M. SANTIAGO, MD, and WILLIAM B. KLAUSTERMEYER, MD, *Los Angeles*

A study was designed to compare the time course response of two high-dose methylprednisolone regimens in adult refractory corticosteroid-dependent asthmatics: Group A received 125 mg intravenously every six hours for three days; group B received 125 mg every six hours for ten days. Sixteen patients during 22 hospital stays were randomly assigned to one of the two groups. Forced vital capacity (FVC), forced expired volume in one second (FEV_1) and forced expiratory flow between 25 percent and 75 percent of vital capacity ($FEF_{25\%-75\%}$) improved significantly over the ten days in both groups ($P<.005$) in all patients. No differences in baseline two-, four-, seven- or ten-day spirometric values were noted between groups ($P>.2$).

In most steroid-dependent asthmatic patients, three days' therapy with 125 mg every six hours of methylprednisolone given intravenously resulted in obvious and sustained ventilatory improvement. Close observation with spirometric and clinical evaluation is then necessary to detect the occasional patient in whom relapse will occur and longer periods of high-dose steroid therapy will be needed.

In 1950 Carryer reported the therapeutic benefits of cortisone in ragweed related asthma.[1] Over the next several years, reports showed the usefulness of corticosteroids in the treatment of asthma.[2-6] Recent reviews of asthma therapy suggest initial doses of from 100 to 1,000 mg of hydrocortisone (or equivalent), followed by a similar range of doses every two to four hours until significant improvement occurs.[7-9] Petty has recommended initial high-dose intravenous steroid therapy in severe, refractory asthma.[10]

We routinely treat patients having severe asthma refractory to bronchodilators with methylprednisolone, 125 mg given intravenously every six hours—a dosage roughly equivalent to those used by Collins and associates.[11,12] Collins (1975) concluded that this dosage range was adequate to treat patients with severe asthma.[11] Few studies,

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however, have provided data comparing dosages or duration of corticosteroid therapy. A preliminary observation suggested that in patients previously treated with corticosteroid a high dose may be required for longer periods than in those who have not had previous steroid therapy.[13] To evaluate the effect of the duration of high-dose steroid treatment, we compared two dosage schedules of intravenously administered methylprednisolone in adult patients with refractory asthma.

Patients and Methods

The study included 16 men during 22 admissions to hospital for severe refractory asthma. Asthma was defined according to the guidelines of the American Thoracic Society as a disease characterized by increased airway resistance that changes in severity either spontaneously or with therapy.[14] Refractory asthma was defined, for the purpose of the study, as perennial airway obstruction not responding to therapy consisting of optimal doses of theophylline compounds, orally administered and aerosolized adrenergic agents, and orally given corticosteroids. All patients had received corticosteroids orally each day with at least 15 mg per day of prednisone (or equivalent). Inhaled beclomethasone dipropionate was used by some of the patients, but was not required as part

TABLE 1.—*Baseline Data in 16 Patients*

Patient	Patient Age (Yr)	Admission Pa_{O_2} (mm Hg)	Admission Pa_{CO_2} (mm Hg)	Identifiable Allergic Component	Duration Asthma (Yr)	Therapy Group A	Therapy Group B
1	61	60*	59	−	38	X	
2	61	68	37	+	10	X	
3	60	55	31	−	5	X	
4	53	85	41	+	8	X	
5	56	69	30	−	4	X	
6	56	110*	26	−	4	X	
7	56	64	51	−	5	X	
8	56	80*	33	−	5	X	
9	56	60	36	−	5		X
10	56	−	−	−	5		X
11	56	57	30	−	5		X
12	51	51	41	+	20	X	
13	51	68	42	+	20		X
14	58	55	47	−	50		X
15	59	65	41	−	25		X
16	60	71	40	+	3		X
17	69	72	32	−	4		X
18	50	88*	42	+	7		X
19	51	43	59	−	4		X
20	49	60	43	−	25		X
21	54	65	35	−	12		X
22	60	62	22	−	2		X

Pa_{O_2} = arterial oxygen pressure
Pa_{CO_2} = arterial carbon dioxide pressure

*Patient receiving supplemental oxygen before arterial blood gas study.

TABLE 2.—*Arterial Blood Gas and Pulmonary Function Test Results at Onset of Study*

Group	Age	Pa_{CO_2} (mm Hg)	Pa_{O_2}* (mm Hg)	FVC (liters) (percent pred.)	FEV_1 (liters) (percent pred.)	$FEF_{25\%-75\%}$ (liters/min) (percent pred.)
A	57	38.8±3.5	71.3±6.1	1.87± .30 (39.0±6.4)	1.02± .19 (30.0±5.5)	33.0±8.3 (16.4±7.7)
B	56	39.1±2.7	63.8±3.2	1.84± .26 (39.7±5.8)	0.93± .13 (28.0±3.7)	26.0±4.5 (13.8±2.3)

P>0.5, except for Pa_{O_2}
±SEM
$FEF_{25\%-75\%}$ = forced expiratory flow between 25 percent and 75 percent of vital capacity
FEV_1 = forced expired volume in one second
FVC = forced vital capacity
Pa_{CO_2} = arterial carbon dioxide pressure
Pa_{O_2} = arterial oxygen pressure

*P>0.1 for Pa_{O_2}. If patients on supplemental oxygen are removed, the difference decreases and P>0.5.

of therapy because it was not commercially available until midway through the study.

All patients were admitted from the hospital's emergency room or the Allergy Clinic to the Pulmonary Acute Care Unit during an acute exacerbation of asthma. After admission patients were treated in a standardized manner: (1) intravenous administration of aminophylline (6 to 9 mg per kg of body weight in a loading dose, and 0.6 to 0.9 mg per kg of body weight per hour by continuous infusion); (2) aerosolized isoetharine; (3) fluids given intravenously; (4) supplemental oxygen by nasal prongs, and (5) methylprednisolone given intravenously. For the first 72 hours all patients received 125 mg of methylprednisolone intravenously every six hours. They were then randomly divided into two groups: in group A therapy was tapered over 48 hours to a single daily dose of 25 to 30 mg of prednisone; in group B the intravenous administration of methylprednisolone was continued for the full ten days. Because of the severity of asthma, it was inappropriate to include a nonsteroid-treated control group. In all patients the intravenous administration of fluids, continuous intravenous aminophylline infusion and use of aerosolized isoetharine were continued for the full ten days. Aminophylline infusion rates were adjusted as needed to maintain serum levels between 1 and 2 mg per dl.

Spirometry was done daily. The ten-day period of study began with the first dose of methylprednisolone. Forced vital capacity (FVC), forced expired volume in one second (FEV_1) and forced expiratory flow between 25 percent and 75 percent of vital capacity ($FEF_{25\%-75\%}$) are reported as percent predicted for age, sex and height using control data from Morris and co-workers.[15] The ages, initial arterial oxygen pressure (Pa_{O_2}) and arterial carbon dioxide pressure (Pa_{CO_2}), and group spirometric data are compared by the unpaired Student t-test for group means. Temporal spirometric changes within a group are evaluated with the paired t-test.

Results

The study was carried out in 16 patients during 22 courses of corticosteroid therapy; in 7 patients for 9 courses in group A (three-day high dose given intravenously) and in 9 patients for 13 courses in group B (ten-day high dose given intravenously). Table 1 presents descriptive data on the patients. There were no apparent differences between the two groups in history of steroid

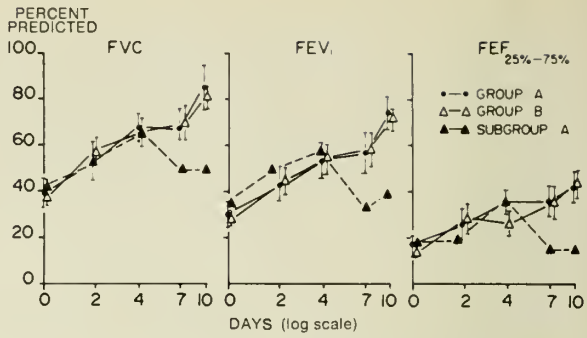

Figure 1.—Group A (three-day high dose) and group B (ten-day high dose) spirometric data during ten-day study. Forced vital capacity (FVC), forced expired volume in one second (FEV_1), and forced expiratory flow between 25 percent and 75 percent of vital capacity ($FEF_{25\%-75\%}$) are presented as percent predicted ± SEM. Dashed line represents two patients in group A with spirometric deterioration when steroid dosage was decreased.

or bronchodilator use, associated rhinosinusitis, allergic component or duration of asthma. Table 2 summarizes the physiologic data at the onset of the study. No statistically significant differences are noted between groups A and B in age, initial Pa_{O_2}, Pa_{CO_2}, or spirometric findings. None of the patients initially or at the time of discharge had pneumonitis or any other febrile illness.

Figure 1 compares the time course of the spirometric response to treatment in groups A and B. Both groups had highly significant improvements in all three measurements from day 0 to day 10 ($P<0.005$). There were no significant differences between the two groups in any of the three measurements on days 0, 2, 4, 7 or 10 ($P>0.2$). Figure 1 also illustrates the ventilatory functions in two patients treated in group A whose conditions deteriorated following the decrease in steroid dose. Until day 4, these two responded favorably, equal to all other patients.

Analysis of the individual data suggests that different temporal patterns of response exist. In some patients ventilatory function improved to a pronounced degree early, followed by a more gradual change. In other patients there was a minimal early response, yet improvement occurred by the tenth day. Ventilatory function improved significantly in each patient during the ten-day study; however, among the patients there was a variation in the rate of improvement and the pattern of change. These variations in temporal response occurred equally in groups A and B. Figure 2 shows data for four patients, illustrating the variation in response among individual pa-

tients. These four patients were studied during more than one acute admission to hospital. Although the initial FVC and FEV_1 varied in patient B, there was a uniform response in each individual patient.

Comment

All patients in our study had clinical and spirometric improvement in ventilatory function while receiving methylprednisolone intravenously with mean flow rates increasing between 200 percent and 300 percent over the ten-day study. For most patients, there was no apparent therapeutic benefit in treating with the high dose methylprednisolone for the full ten days when compared with three days. This finding is consistent with a previous report by Britton and co-workers (1970) comparing three dosage schedules by following peak expiratory flow rates (PEFR) over an eight-day period (his high dose was roughly equivalent to that used for group A).[16] In both studies it was assumed that corticosteroids are necessary for therapy; therefore, untreated control groups were not studied.

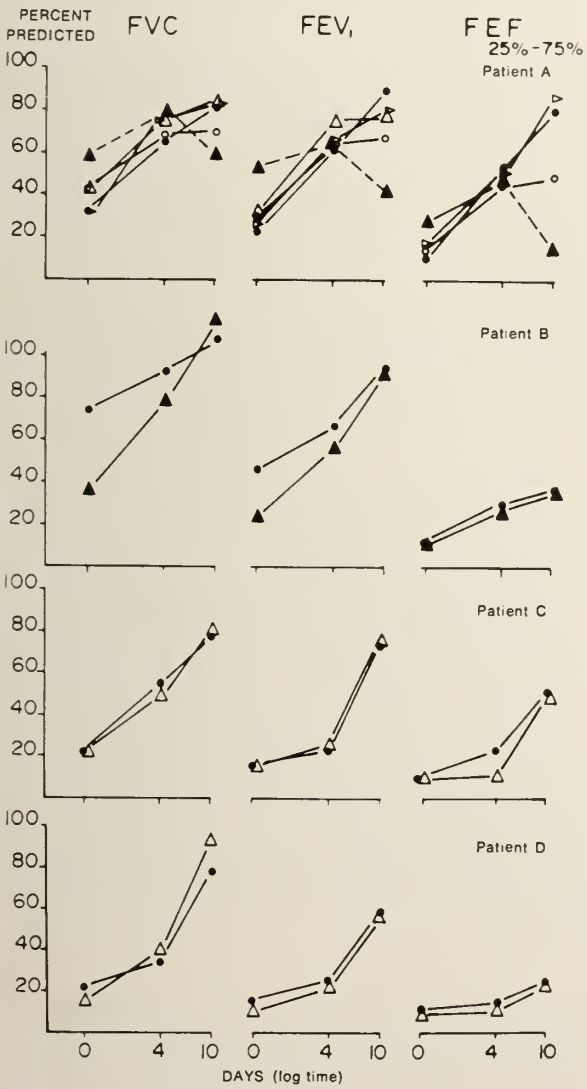

Figure 2.—Summary data from four patients illustrating different patterns of improvement between patients, but individual patient uniformity on repeated studies. Solid symbols represent group A protocol; open figures represent group B protocol.

It has been noted that in cases of acute exacerbations of asthma, the altered pulmonary physiology and response to therapy differ from patient to patient.[17,18] The duration of ventilatory obstruction following an acute attack is not clearly established, but may be days to weeks.[19] Despite the apparent clinical uniformity of our study patients, we noted several patterns of improvement in ventilatory function. Although some patients had normal pulmonary function by ten days, most had a persistent degree of obstruction. Because of the chronic severe nature of the asthma in our patients, it is not surprising that significant degrees of obstruction were apparent in some patients at the end of the study period. The design in our study did not allow evaluation beyond ten days.

Ellul-Micallel and Fenech (1975)[20] and Klaustermeyer and Hale (1976)[13] in stable chronic asthmatic patients showed significant improvements in maximal expiratory flow at 50 percent vital capacity from the flow volume curve, specific conductance, peak expiratory flow (PEF), FVC, FEV_1, $FEF_{25\%-75\%}$ between two and six hours following a single injection of corticosteroid. In contrast to the acute responses in patients with stable chronic asthma, McFadden and co-workers (1976) were not able to show corticosteroid effects on ventilatory function over six hours in extrinsic asthmatic patients.[21] Pierson and associates (1974) in a double-blind study, followed the conditions of children for 24 hours during acute asthma.[22] Although they found no spirometric benefit from the steroid therapy, they noted significant improvement in Pa_{O_2} in the steroid treated group over controls. In both studies, findings were near normal on pulmonary function tests by the end of the study, in contrast with results in our patient population.

The individual variability in initial response (day 4) and in maximal degree of improvement (day 10) was large in our patients. This variability suggests underlying physiologic differences between patients not apparent by our present

methods of evaluating and classifying asthmatic persons. The duplicate studies in four patients, however, suggest that a given person is likely to respond to steroids in a similar manner with each attack. The uniformity in response to treatment in an individual patient appears independent of the steroid schedule used. Woolcock and Read (1966) clearly showed in spontaneous asthma many patterns of flow rate and lung volume changes, and an apparent uniformity in the alterations in repeat examination in individual patients.[23]

Both dosage schedules used in this study may be more than adequate to treat most patients with severe asthma. However, it is significant that in two patients in group A (treated with three days of high dose methylprednisolone) there was clinical and spirometric deterioration between days 4 and 10 when the steroid dosage was decreased. This suggests that the three-day high dose regimen was inadequate in these two cases. In both patients suffering relapses, the relapse occurred after a significant initial improvement in ventilatory function.

Concern for potential idiosyncratic and toxic side effects motivates studies of minimal dose and duration of corticosteroid. High doses of intravenously given methylprednisolone have been implicated in sudden death, arrhythmias, hyperglycemia, hypokalemia, sodium retention, hypertension, increased infectious complications, acute gastrointestinal bleeding, pancreatitis and acute psychosis.[24-26] We observed none of these complications in this study.

Early intervention with adequate doses of corticosteroids should begin as soon as bronchodilator unresponsiveness is identified in all seriously ill adult asthmatic patients. A dosage of 125 mg of methylprednisolone given every six hours intravenously (or its equivalent) is adequate and data supporting adequacy of lower dosages are not yet available. In most patients, this therapy results in obvious and sustained ventilatory improvement within three days. Close observation is then mandatory to detect the occasional case in which relapse will occur and in which longer periods of high-dose corticosteroid therapy will be required.

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Cushing Syndrome

Current Concepts of Diagnosis and Therapy

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A variety of diagnostic advances including radioimmunoassay of adrenocorticotropic hormone (ACTH) have increased the number of methods for laboratory investigation of Cushing syndrome. However, experience with these procedures has led to a recognition of their limitations. We have developed an algorithm which incorporates these newer techniques and minimizes the number of procedures required to diagnose the various causes of Cushing syndrome. At present, we recommend pituitary surgical operations for pituitary-dependent Cushing syndrome because we believe this disease is caused by the development of a pituitary ACTH-secreting tumor.*

SEVERAL NEW DEVELOPMENTS in our approach to the diagnosis and treatment of cortisol excess combine to make a review of this subject timely. New variants of hypercortisolism including periodic rhythmic secretion of adrenocorticotropic hormone (ACTH) and an array of extrapituitary sources of ACTH have necessitated revisions of the algorithm for diagnostic evaluation of patients in whom Cushing syndrome* is suspected. The increasing availability of plasma ACTH assays for both "big" and "little" forms of the hormone raises questions as to the pragmatic application of plasma ACTH determinations in the differential diagnosis of various manifestations of the Cushing syndrome. Finally, a recent flurry of interest in pharmacological and microsurgical treatments of Cushing disease has stimulated reappraisals of the choices of therapy for pituitary-dependent hypercortisolism.

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*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

Pathophysiologic Classification

The various known causes of Cushing syndrome are listed in Table 1. Undoubtedly, the most common cause of Cushing syndrome is the use of exogenous glucocorticoids for a variety of disorders. We will not discuss the presentation of this syndrome except to say that it does not differ basically from other causes of endogenous hypercortisolism.

Clinical features depend on the steroids being produced. Adrenal adenomas frequently present with florid Cushing syndrome. Often the adenomas produce few if any steroids other than cortisol. The result of this relatively pure cortisol secretion is considerable depletion of protein. Often patients with pure cortisol-secreting adrenal adenomas will lack signs of concomitant androgen secretion such as hirsutism, acne formation and

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
17-KS = 17-ketosteroids
17-OHCS = 17-hydroxycorticosteroids

oily skin. Lack of adrenal androgen secretion, which appears to attenuate cortisol effects, leads to a syndrome of pronounced glucocorticoid effects. Standard tests may show only modestly elevated indices of cortisol secretion in some patients with adrenal adenoma, which provide a clue to the pathogenesis. Frequently, urinary 17-ketosteroids (17-KS) determinations are within normal range, suggesting that few adrenal androgens are being secreted.

In sharp contrast to patients with adrenal adenoma, those with adrenal carcinomas often produce biologically active steroids other than cortisol. Most commonly these steroids are androgens, but excess estrogens and mineralocorticoids have been reported.[1] It is not unusual for adrenal cancers to produce weak adrenal androgens in great quantities. If urinary 17-ketosteroids are greater than 100 mg per 24 hours in the presence of Cushing syndrome, the cause is most probably cancer of the adrenal glands.

Spontaneous clinical remissions of adrenal adenomas,[2] but not carcinomas, have been reported. However, the possibility of periodic secretion cannot be excluded in such cases.

Endogenous hypercortisolism is most often caused by excess pituitary ACTH secretion. We prefer the designation used by Tyler and West,[3] pituitary-dependent Cushing syndrome, because it encompasses a variety of possible etiologic mechanisms mediated by pituitary ACTH. Central nervous system causes have been suggested by indirect lines of evidence. One such experiment involves use of cyproheptadine, a serotonin antagonist, to treat pituitary-dependent Cushing syndrome. Successful therapy with this agent, as reported in some studies,[4] would suggest that interruption of abnormal central nervous system stimulation of the pituitary is all that is necessary to control abnormal ACTH secretion. Other investigators,[5] however, have not found this form of therapy effective.

The most compelling reason to implicate a central nervous system cause is the absence of a pituitary tumor in about 20 percent of cases of pituitary-dependent Cushing disease. Most pathologic studies, however, occurred before knowledge of the *ectopic* ACTH syndrome,[6] and many such cases described without evidence of a pituitary tumor could have represented examples of this syndrome. Besides the possibility of a mistaken pathologic diagnosis due to ectopic sources of ACTH, is the fact that small microadenomata can cause Cushing disease. Such tiny tumors might be easily overlooked at autopsy. Recently, a microadenoma in an *empty sella* has been described as a cause of this disorder.[7] In clinical situations where a pituitary tumor and ectopic ACTH secretion have been reasonably excluded, a central nervous system cause is suggested.

TABLE 1.—*Causes of Cushing Syndrome*

Exogenous steroid administration
Pituitary-dependent Cushing syndrome
Without demonstrable tumor
With demonstrable tumor
Multinodular adrenal hyperplasia
Adrenocortical tumors
Adenoma
Carcinoma
Ectopic ACTH-producing tumors

ACTH = adrenocorticotropic hormone

On the other hand, pituitary-dependent Cushing disease has been cured by removal of a pituitary adenoma;[8] the subsequent recovery of normal pituitary-adrenal function provides strong evidence that the central nervous system did not cause the disease. At this time, multiple causes of pituitary-dependent Cushing syndrome remain possible and await further studies. Interestingly, although Harvey Cushing is often quoted as suggesting that pituitary tumor is the cause of the disease named after him, he speculated cautiously because in only six of his eight cases was a tumor identified.[9]

Nodular hyperplasia of both adrenal glands is a rare cause of Cushing syndrome. These patients have substantially enlarged adrenal glands which usually respond to ACTH but do not usually respond to metyrapone or dexamethasone suppression. Hidai and co-workers[10] have observed a patient with nodular hyperplasia, in whom the total weight of both adrenal glands was 161 grams. We have observed a previously unreported patient with the same condition whose combined adrenal glands weighed 229 grams. These patients had ACTH detectable in plasma when untreated, and ACTH plasma concentrations greater that normal after bilateral adrenalectomy and replacement cortisol therapy.[10] Data from these

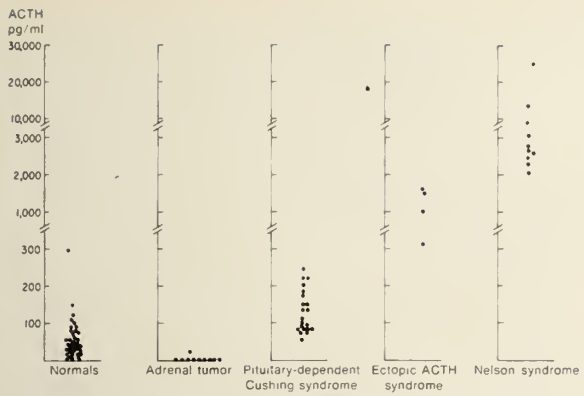

Figure 1.—Plasma ACTH concentrations of patients with various disorders affecting ACTH secretion. (ACTH= adrenocorticotropic hormone)

cases suggest a dual control mechanism: first, a source of excess ACTH which orginates from the pituitary and leads to adrenal hyperplasia. Later, some areas of hyperplastic adrenal tissue become autonomous. Such a pathogenesis would lead to nonsuppressibility and account for supraphysiologic ACTH concentrations in patients who are receiving replacement cortisol after adrenalectomy.

There are innumerable types of nonpituitary tumors that secrete ACTH and cause the ectopic ACTH syndrome. Carcinoma of the lung is, by far, the most frequent source, followed by cancer of the pancreas and thymus.[11] Most tumors that secrete ectopic ACTH do so with apparent absolute autonomy; however, a few tumors such as thymus and bronchial carcinoids have been suppressible with dexamethasone.[12,13] The ACTH molecule secreted by nonpituitary sources appears to be identical to the authentic 39 amino acid pituitary ACTH. One group,[14] however, has reported a thymic tumor with an abnormal ACTH molecule, apparently made up of the 2-38 amino acid sequence. Others have suggested that "big" ACTH may be a circulating marker for ectopic sources of ACTH.[15] Because the larger ACTH molecule is far less active biologically than the usual 1-39 smaller molecule, it may circulate in high concentrations without producing clinical signs or symptoms. Sampling "big" ACTH at regular intervals in patients at high risk for the development of a malignant condition (such as heavy smokers in whom cancer of the lung might occur), may help to detect tumors in an early stage of development. Further experience with large ACTH molecules is necessary before a routine assay in the blood can have wider applications than use in research studies.

Finally, there are recent reports of large amounts of ACTH present in nontumorous lung tissue taken from sites remote from the tumors in patients with lung cancer, suggesting the possibility that the ectopic ACTH syndrome may not be a simple disorder of tumor hormone production.

Plasma ACTH Determinations

Several commercial laboratories now offer the plasma ACTH radioimmunoassay. It is not generally available in clinical pathology laboratories, though some university centers carry out the test on a research basis. Sufficient information has been accumulated to outline general rules regarding the clinical application of plasma ACTH determinations:

(1) *Two or more samples should be obtained to estimate the mean plasma ACTH.* The diurnal variation of plasma ACTH, its short half-life in plasma and the fact that it is secreted in pulsatile bursts[16] contribute to its widely and rapidly varying concentrations in plasma. Occasionally, ACTH may be undetectable in a single specimen from a normal person as well. Thus, in distinguishing normal from low levels, multiple specimens are helpful.

(2) *Plasma ACTH determinations are not useful in distinguishing normal subjects from those suspected of having pituitary-dependent Cushing disease.* Several groups have found that the mean value of random plasma ACTH concentrations in untreated pituitary-dependent Cushing disease is about 100 pg per ml.[17,18] This value overlaps the upper end of the normal range precluding the use of the determination as a screening tool (Figure 1).

(3) *Plasma ACTH determinations appear to be useful in distinguishing adrenal tumor-dependent versus ACTH-dependent hypercortisolism.* ACTH is rarely detectable in multiple specimens from patients with adrenal tumor-dependent disease and almost always detectable in specimens from persons with ACTH-dependent disease. Furthermore, *resting* plasma ACTH values in excess of 500 pg per ml in untreated patients with hypercortisolism are highly suggestive of the ectopic ACTH syndrome.[1,17]

(4) *Care in collection and preservation of plasma specimens is important.* ACTH bioactivity disappears promptly from plasma at room temperature due to enzymatic degradation of the hormone.[19] While immunoreactivity necessary for the radioimmunoassay is hardier than bioactivity, it

TABLE 2.—*Shortcomings of Methods of Estimating Cortisol*

Methods	*Sources of Error, Variability or Nonspecificity*
Plasma cortisol by radioimmunoassay	Diurnal variation. Episodic variation due to pulsatile secretion. Binding protein (transcortin) variations.
Plasma cortisol by fluorescence	Shortcomings listed above plus interfering substances, especially spironolactone (Aldactone). Many fluorescent steroids.
Urinary 17-OHCS (Porter-Silber)	Collection errors. Interfering substances.
Urinary 17-ketogenic steroids	Less specific than 17-OHCS.
Urinary 17-ketosteroids (17-KS)	Nonspecific. Only 5 percent of cortisol is excreted as 17-KS.
Urinary "free" cortisol	Suboptimal specificity. Also measures 11-deoxycortisol and other corticosteroids. Not well standardized.

17-OHCS = 17-hydroxycorticosteroids

too will disappear after several hours at room temperature. Accordingly, collection and refrigeration of blood and the prompt separation of plasma is essential for obtaining valid results. Furthermore, ACTH is readily adsorbed to glass. While the protein content of plasma helps prevent such adsorption it is wise to use plastic containers for collection and shipping of specimens.

(5) *"Big" ACTH determinations and lipotropins.* Evidence exists that ACTH is a portion of a precursor molecule consisting of approximately 260 amino acids referred to as "big" ACTH. Lipotropin is considered a part of this precursor molecule as well.[20] Plasma ACTH levels determined by radioimmunoassay in the ectopic ACTH syndrome are generally higher than in pituitary-dependent Cushing syndrome.[21,22] The lack of substantially elevated cortisol production in association with these extremely high plasma ACTH determinations in the ectopic syndrome suggest secretion of an intact precursor molecule without biological activity. Chromatographic studies have supported this idea.[21,22]

Lipotropin secretion seems to parallel ACTH secretion, which is consistent with the concept of a common precursor molecule.[23] So far, no pattern of ACTH, "big" ACTH or lipotropin secretion has allowed separation of the ectopic ACTH syndrome from pituitary-dependent Cushing syndrome. Further experience with specific assays for ACTH, lipotropin and intact precursor molecules in the future may permit distinguishing the ectopic syndrome from pituitary-dependent Cushing disease.

Measurements of Cortisol

Knowledge that cortisol secretion varies episodically as well as diurnally has served to reinforce the opinion that quantitative clinical estimates of cortisol secretion are best made by measuring cortisol from its metabolites in 24-hour urine collections rather than in random specimens of plasma. Several methods appear to have stood the test of time, and no one seems clearly better than the others, either on a theoretical or practical basis. Table 2 lists available tests requiring 24-hour collection and tabulates the normal excretion values. Some investigators have advocated expression of cortisol values as a function of creatinine excretion or surface area, but we have not found this to be particularly helpful because we place more diagnostic emphasis on suppression or stimulatory manipulations of cortisol excretion rather than on basal values per se. For example, urinary 17-hydroxycorticosteroid (17-OHCS) excretion of 12 mg per 24 hours is a slightly elevated value. Whether or not that basal value exceeds normal limits for a patient is not as important as whether or not the value remains stable for several days.

While the urinary 17-hydroxycorticoid test and the measurement of 17-ketogenic steroids and urinary 17-ketosteroids all reflect excretion of cortisol metabolites, urinary 17-OHCS determinations permit the most specific measurement. Approximately 25 percent to 33 percent of cortisol is excreted as a urinary 17-OHCS in normal subjects, while only 20 percent of 17-ketogenic steroids are derived from cortisol and only 5 percent of cortisol metabolites are 17-ketosteroids. Conversely, only the major steroids cortisol and Compound S metabolites contribute to the 17-OHCS, while numerous other steroids contribute to both 17-ketosteroid and 17-ketogenic determinations.[24]

Urinary Free Cortisol

Free cortisol is commonly understood to represent unmetabolized and unconjugated cortisol. Approximately 0.2 percent of cortisol secreted by adrenal glands is excreted in this form. Urinary

free cortisol appears to be of greatest value as a screening test for hypercortisolism.[25] Two prior shortcomings have limited its wider application. First, the test is not well standardized and considerable overlap of values exists in published reports between suspected and proved cases of Cushing syndrome. Second, the test is relatively nonspecific because reported methods also detect compound S, corticosterone and sometimes progesterone.

Diagnosis of Cushing Syndrome

Referral for diagnostic evaluation of possible Cushing syndrome is generally made because of physical stigmata suggesting hypercortisolism, elevated 24-hour urinary 17-hydroxycorticosteroid excretion, elevated urinary free cortisol concentration or abnormal overnight dexamethasone suppression test. We continue to use overnight dexamethasone suppression as a screening test rather than as part of the definitive diagnostic evaluation. False-positive results (8 AM plasma cortisol of greater than 5 μg per dl after receiving 1 mg of dexamethasone at midnight) can misidentify normal, obese persons as having Cushing syndrome[26] if such testing is substituted for standard low-dose dexamethasone suppression (0.5 mg given every six hours for two days.)[26]

As a practical approach, patients with suspected Cushing syndrome are given the standard low-dose dexamethasone test on an outpatient basis and, if positive, are admitted to the hospital for further testing. Duplicate aliquots of all specimens are stored in a refrigerator on the ward in the event that any are mishandled or lost. To measure basal urinary 17-OHCS and 17-ketosteroids (17-KS), urine specimens are collected on days 1 and 2. Urinary 17-OHCS determinations alone are done during the remainder of the testing period. Metyrapone, 750 mg every four hours in six dosages is administered on day 3. The maximum rise of the urinary 17-OHCS in response to metyrapone is somewhat unpredictable and can occur during either the day of or the day after administration of metyrapone; therefore, no manipulations are done on day 4. Dexamethasone, 0.5 mg every six hours (low dose) is given on days 5 and 6, followed by 2 mg every six hours (high dose) on days 7 and 8.

An algorithm of our diagnostic approach to Cushing syndrome and its interpretation are given in Figure 2. The literature reflects some confusion about interpretation of the low-dose dexamethasone test. As Liddle originally described, values of urinary 17-hydroxycorticosteroids fall to less than 3 mg per 24 hours on the second day of administration of dexamethasone (0.5 mg every six hours).[27] Values above this level are strongly suggestive of Cushing syndrome if the urine collection was accurate and if the patient is not tak-

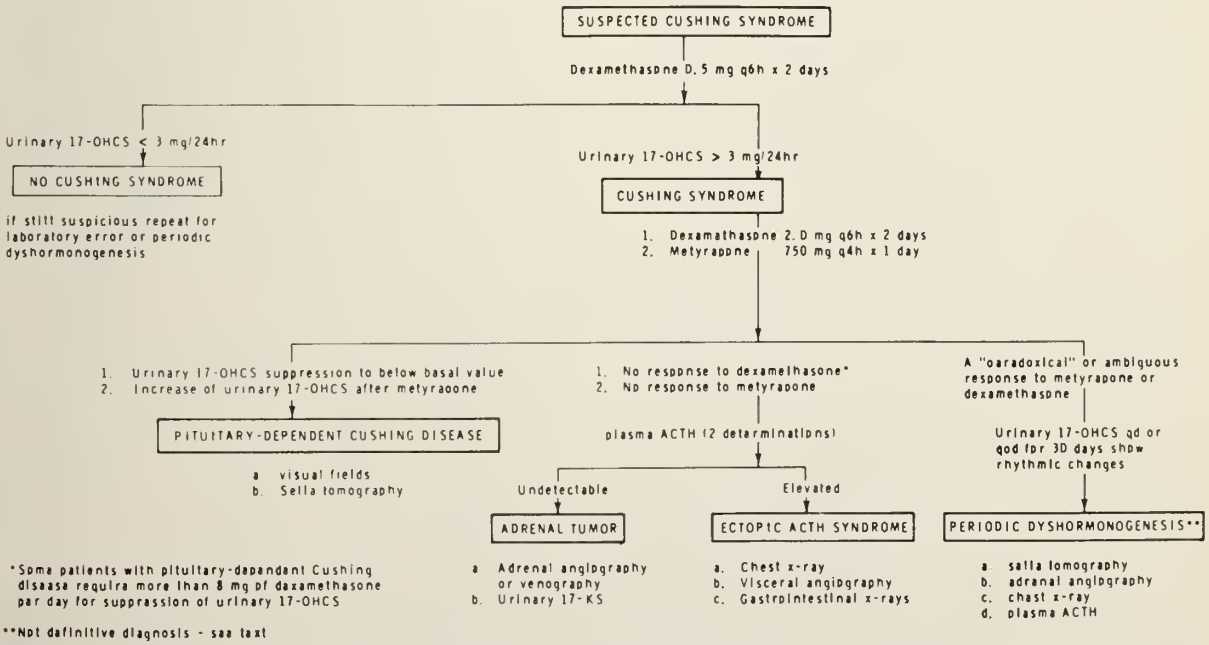

Figure 2.—Chronologic sequence of procedures suggested to identify and diagnose hypercortisol syndromes. (ACTH = adrenocorticotropic hormone; 17-KS = 17-ketosteroids; 17-OHCS = 17-hydroxycorticosteroids)

ing other drugs that might alter cortisol or dexamethasone metabolism.

Table 3 shows suppression test results in a patient with classic features of Cushing disease. The initial test results were interpreted as "normal in an obese patient." Two years later the test results were obviously abnormal. It is probable that the initial suppression values were also abnormal, but not properly interpreted. Suppression of the urinary 17-OHCS to less than 3 mg during low-dose dexamethasone testing is within normal limits, and is strong evidence against the presence of Cushing syndrome. Lack of a normal response usually confirms the diagnosis of Cushing syndrome but does not distinguish between various causes. With high-dose dexamethasone administration the urinary 17-OHCS will usually suppress to less than half the basal values in pituitary-dependent Cushing syndrome. This reflects a disordered cortisol feedback in which ACTH secretion remains responsive to the suppressive effects of cortisol although higher circulating concentrations are required. Occasionally, a more pronounced feedback abnormality is seen in patients with pituitary-dependent Cushing syndrome in whom no suppression of the urinary 17-OHCS to standard high-dose dexamethasone testing is observed. A fall of the urinary 17-OHCS will occur however, if very large dosages of dexamethasone (8 mg every six hours) are used (Table 4). Such responses seem to indicate that a wide variation in degree of feedback abnormality exists in pituitary-dependent Cushing syndrome.

TABLE 3.—*Results of Urinary 17-OHCS Suppression Tests in a Patient With Classic Features of Cushing Syndrome*

Date	*Drug Dosage*	*Urinary 17-OHCS (mg/24 hrs)*
1962	None	16
1962	Second day of dexamethasone 0.5 mg every six hours	7
1964	None	21
1964	Second day of dexamethasone 0.5 mg every six hours	13
1965	None	25
1965	Second day of dexamethasone 0.5 mg every six hours (low dose)	19
1965	Second day of dexamethasone 2.0 mg every six hours (high dose)	8

17-OHCS = 17-hydroxycorticosteroids

Metyrapone administration results in a significant increase of the urinary 17-OHCS in pituitary-dependent Cushing syndrome. This agent is primarily an 11β-hydroxylase inhibitor and causes an increase of plasma 11-desoxycortisol levels with a fall of the plasma cortisol concentration. A lowering of the cortisol levels coupled with the negligible ACTH-suppressive activity of 11-desoxycortisol results in increased ACTH secretion. Because 11-desoxycortisol is metabolized to a 17-OHCS, urinary 17-OHCS increases (Figure 3). Routine use of metyrapone is valuable for confirmation of pituitary-dependent Cushing syndrome, especially in patients with resistance to high-dose dexamethasone.

Patients with pituitary-dependent Cushing syndrome should be evaluated for a pituitary tumor with sellar tomography. These findings are usually negative in an untreated case. If a pituitary tumor is present, tests to exclude the possibility of suprasellar extension should be done because knowledge of this complication's presence is critical for selection of an appropriate treatment modality.[28] Findings on visual field examination and pneumoencephalography as well as an elevated cerebrospinal fluid (CSF) ACTH concentra-

TABLE 4.—*Response of Urinary 17-OHCS to Large-Dose Drug Therapy in a Patient With Pituitary-Dependent Cushing Syndrome*

Day	*Drug Dosage*	*Plasma ACTH (pg/ml)*	*Plasma Cortisol (µg %)*	*Urinary 17-OHCS (mg/24 hrs)*
1	None	150	38	29
2	Metyrapone	248	24	48
3	None	176	32	44
4	Dexamethasone (2 mg per day)	170	26	41
5	Dexamethasone (2 mg per day)	105	26	42
6	Dexamethasone (8 mg per day)	86	19	23
7	Dexamethasone (8 mg per day)	116	10	26
8	Dexamethasone (32 mg per day)	43	21	23
9	Dexamethasone (32 mg per day)	<30	4.9	10
10	ACTH infusion (50 units per day)	...	...	199

ACTH = adrenocorticotropic hormone
17-OHCS = 17-hydroxycorticosteroids

tion are all valuable indicators of suprasellar extension. An elevated cerebrospinal fluid ACTH concentration with suprasellar extension presumably results because the tumor invades the subarachnoid space and releases hormone directly into CSF. Patients with ACTH-secreting tumors without suprasellar extension have cerebrospinal fluid ACTH levels less than 200 pg per ml despite striking elevation of the plasma ACTH concentration (up to 6,000 pg per ml).[28,29]

Computerized axial tomographic (CAT) scanning is a relatively new tool and, therefore, extensive experience in its use has not been generated. In a recent study,[30] CAT scanning detected all 17 pituitary tumors greater than 1.5 cm in size, three of five between 1.5 and 0.5 cm and none less than 0.5 cm. This experience coupled with our own suggests that small pituitary tumors with minimal suprasellar extension can be more accurately identified by pneumoencephalography than by CAT scanning.

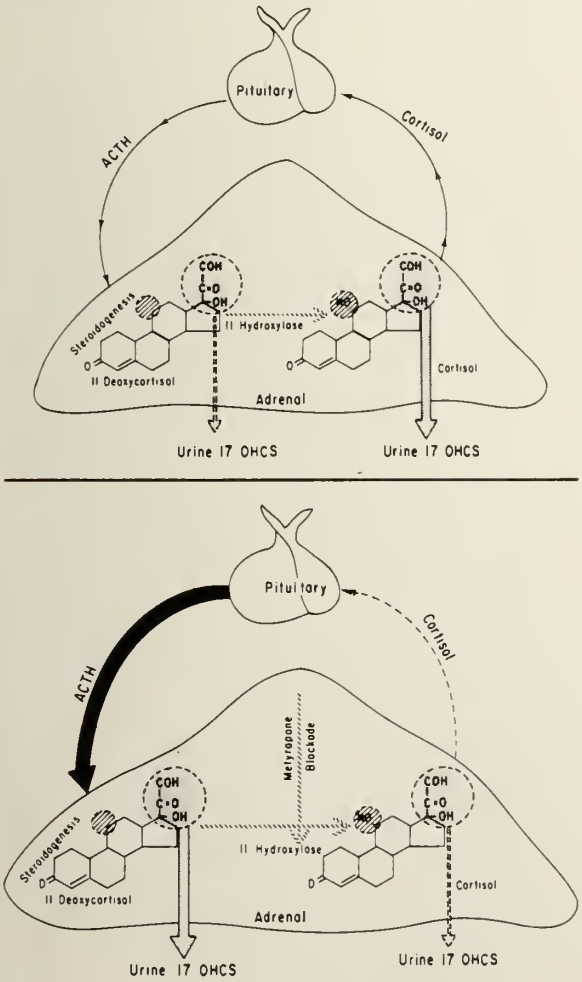

Figure 3.—Metyrapone blockade of adrenal steroidogenesis **(top)**. Because the urinary 17-OHCS test does not discriminate between the precursor to cortisol (11-desoxycortisol) and cortisol, a rise of urinary steroids indicates an intact pituitary adrenal axis **(bottom)**.

Characteristically, patients with a cortisol-secreting adrenal tumor or ectopic ACTH secretion show no change of the urinary 17-OHCS during either low- or high-dose dexamethasone suppression or with metyrapone stimulation. This would be expected because the hypercortisolism is not dependent upon pituitary ACTH secretion. Neither of these maneuvers, therefore, can distinguish patients with ectopic ACTH secretion from those with adrenal tumors. Occasionally, however, the urinary 17-OHCS will fall after metyrapone administration in cases of adrenal tumor. The paradoxical response is probably explained by the dual sites of inhibition of adrenal steroidogenesis exhibited by metyrapone.[31] This drug blocks not only 11β-hydroxylation but also cholesterol cleavage in the *absence* of ACTH. With ACTH present the block of cholesterol cleavage induced by metyrapone is overcome; however, the 11β-hydroxylation block remains.[31] Thus, in states of hypercortisolism without circulating ACTH (adrenal tumors) a block early in steroidogenesis, such as cholesterol cleavage, would cause a fall of urinary 17-OHCS. Additionally, routine measurement of urinary 17-OHCS detects cortisol metabolites more effectively than 11-desoxycortisol metabolites.

More reliably, patients with ectopic ACTH secretion and adrenal tumors can be distinguished from those with pituitary-dependent Cushing disease by measurement of plasma ACTH concentration. Figure 1 shows ACTH concentrations in patients with Cushing syndrome who were evaluated at the University of Oregon Health Sciences Center. Plasma ACTH is almost always undetectable in patients with adrenal tumors. However, one patient with a surgically documented cortisol-secreting adrenal adenoma had low but definitely measurable ACTH in plasma. We have no explanation for this observation. In contrast, patients with ectopic ACTH secretion have plasma ACTH levels that are elevated, often exceeding 1,000 pg per ml. In pituitary-dependent Cushing syndrome the plasma ACTH is usually at or somewhat above the upper limits of normal (110 pg per ml). The highest levels of ACTH that we have observed are in patients with Nelson syndrome. In this condition deep pigmentation with substantially elevated plasma ACTH levels develop after bilateral adre-

nalectomy for pituitary-dependent Cushing syndrome. In most of these patients a large pituitary tumor can be observed. As previously emphasized, at least two plasma ACTH determinations should be done before any diagnostic conclusions are made.

If tests result in undetectable plasma ACTH levels associated with unresponsive urinary 17-OHCS to dexamethasone and metyrapone, or a paradoxical fall of urinary 17-OHCS with administration of metyrapone, a patient has an adrenal tumor. Several varieties of radiologic investigation can then be used for locating the tumor. Large tumors can frequently be detected by intravenous pyelography and tomography. Adrenal venography or selective adrenal arteriography, however, is usually required to find smaller lesions.[32,33] Adrenal scanning with radioiodinated cholesterol can visualize benign adrenal tumors; however, adrenal carcinomas usually cannot be visualized.[34] This noninvasive technique holds promise for the future but is not yet widely available. Differentiation of a benign adenoma from carcinoma can be difficult on the basis of clinical characteristics or radiologic appearance. A basal urinary 17-KS determination, however, of greater than 100 mg is suggestive of a malignant adrenal tumor, and a value greater than 200 mg is pathognomonic for adrenal carcinoma.

Levels of urinary 17-OHCS that are unresponsive to dexamethasone and metyrapone and are accompanied by a high plasma ACTH concentration strongly suggest ectopic ACTH secretion. The most common tumors associated with this syndrome are carcinoma of the lung, pancreatic cancer, thymoma and bronchial adenomas.[11] A careful and exhaustive search using appropriate radiographic studies is indicated in any patient with suspected ectopic ACTH secretion.

A recently described entity is Cushing syndrome with periodic hormonogenesis.[35-38] In this unusual variant, rhythmic fluctuations of ACTH result in a cyclic rise and fall of the urinary 17-OHCS. The causes of the Cushing syndrome in the four previously described cases were a pituitary tumor in two[36,38] and a bronchial adenoma in the other two.[35,37] The durations of the cycles were approximately 7, 11, 18 and 86 days. We recently evaluated a patient with pituitary-dependent Cushing disease and periodic hormonogenesis (Figure 4) and the cycle duration was 7.5 days. Unfortunately, the rapid progression of the patient's disease precluded more extensive studies. It is very likely that the phenomenon of periodic hormonogenesis accounts for earlier reports of paradoxical responses to dexamethasone.[36] If dexamethasone is given during a phase of increasing cortisol secretion, a *paradoxical response* will be observed. In addition, if dexamethasone is given during a period of decreasing cortisol secretion, test results may be misinterpreted as suppression. Metyrapone given either during an ascending or descending phase of the cycle also could result in misleading or confusing laboratory findings. Periodic hormonogenesis can be established only by sequential urine collections.

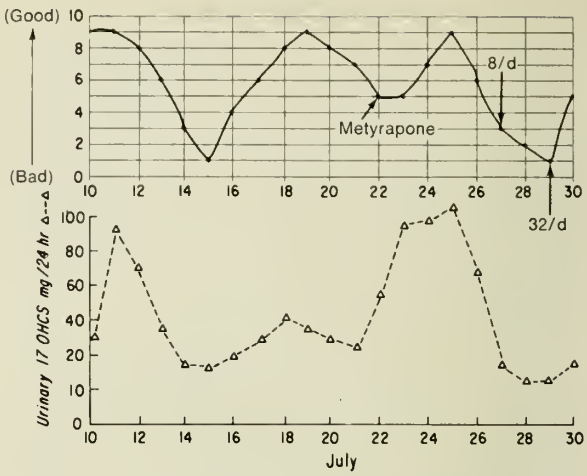

Figure 4.—Fluctuations in sense of well-being correlated with daily urinary 17-OHCS determinations in a 29-year-old man with Cushing syndrome and periodic dyshormonogenesis. (Top graph was constructed by the patient who, at the time, was unaware of urinary steroid values.)

Several other unusual situations can cause confusion in the diagnosis of Cushing syndrome and deserve mention. Suppression of cortisol secretion with higher doses of dexamethasone can occur in patients with ectopic ACTH secretion from a bronchial adenoma.[14] Whether this response is actually due to periodic hormonogenesis is uncertain. Fluctuation of cortisol secretion also occurs in patients with Cushing syndrome and micronodular adrenal hyperplasia, although definitive cyclic variation has not been described.[39] In micronodular hyperplasia there are periods when the urinary 17-OHCS excretion is within normal limits; however, the urinary free cortisol concentration at these times will be elevated.[39] Such patients are usually young and do not have clinical stigmata of Cushing disease. This condition frequently presents as idiopathic osteoporosis. Recently, it

has been recognized that long-term alcohol abuse can produce an excess glucocorticoid appearance associated with abnormal (1 mg dexamethasone at midnight) suppression of plasma cortisol.[40,41] In addition, urinary 17-OHCS excretion can remain abnormally elevated during standard low- and high-dose dexamethasone suppression simulating an adrenal tumor or ectopic ACTH secretion (Jordan, unpublished observations). These abnormalities, however, resolve after withdrawal of alcohol. It is apparent that a history of alcoholism must be sought in a patient with suspected Cushing syndrome if misdiagnosis is to be avoided. Similar resistance to cortisol suppression has been reported in depression which reverts to normal levels after treatment.[42]

Finally, several drugs are capable of affecting the results of a diagnostic evaluation of Cushing syndrome. Diphenylhydantoin is known to accelerate the metabolism of both dexamethasone and metyrapone and this can result in anomalous test results.[43,44] Spironolactone and testosterone can elevate while estrogens can cause spuriously low readings of the urinary 17-OHCS.[45,46] Administration of the following medications also results in alterations of the urinary 17-OHCS: acetazolamide, chloral hydrate, chlorothiazide, chlordiazepoxide, colchicine, dextroamphetamine, digitoxin, digoxin, glutethimide, iodides, meprobamate and oleandomycin.[45,46] A systematic review of drugs affecting pituitary adrenal function tests has been made elsewhere.[47]

Therapy for Cushing Syndrome

Therapy for pituitary-dependent Cushing syndrome remains the most controversial aspect of treatment of hypercortisolemic states. Selection of therapeutic modality has been influenced heavily by local availability of techniques such as neurosurgery or radiation and the fact that no one treatment plan has emerged as uniformly successful. As a result, a plethora of modalities have been used to treat this disorder. The most commonly used therapies have been total bilateral adrenalectomy, conventional or heavy particle pituitary radiation, implantation of radioactive seeds in the anterior pituitary, pharmacologic treatment and, more recently, transsphenoidal surgical procedures to pituitary tumors.

Total bilateral adrenalectomy provides the quickest means of relieving pituitary-dependent hypercortisolism. Some patients, however, cannot tolerate this procedure due to extreme debility associated with the disease or unrelated reasons. Surgical considerations such as severe furunculosis secondary to hypercortisolism, refractory to antibiotic and local therapy, also preclude operation because postoperative wound infection is a concern in these circumstances. An adrenal operation requires, at present, total bilateral adrenalectomy. Previous attempts at partial resection have been unsuccessful because there is at least a 30 percent recurrence rate[48,49] of hypercortisolism. To avoid replacement corticosteroid therapy necessitated by total bilateral adrenalectomy, adrenal autotransplants have been attempted.[50,51] However, we are not aware of any reported successes with this procedure of placing small pieces of adrenal gland into muscle or fat. The use of finely diced pieces of tissue such as has been used for parathyroid autotransplantation of hyperplastic tissue[52] has not been attempted with adrenal tissue.

Patients who receive bilateral adrenalectomy as therapy for Cushing disease are not cured of the pituitary component of the disease. Nelson and colleagues first described[53] the syndrome which bears his name in which hyperpigmentation and a pituitary tumor developed after bilateral adrenalectomy for Cushing syndrome. The condition has been called Nelson syndrome, and its incidence is estimated at 8 percent[54] following bilateral adrenelectomy. Our experience, contrary to that of Moore and co-workers,[54] is that these tumors are particularly aggressive, subject to spontaneous infarction and frequently necessitate a combination of therapeutic approaches such as both pituitary surgical procedures and irradiation to achieve control.[18] The thrust of initial therapy, then, should be twofold—cure the hypercortisolism and prevent or control other deleterious effects of a probable pituitary tumor. We believe that all patients with pituitary-dependent Cushing disease should be treated as if they were harboring a pituitary tumor. Our studies of pituitary ACTH secretion before and after bilateral adrenalectomy support this idea.[18]

We have found that ACTH secretory dynamics are qualitatively similar before adrenal operations and after development of a definite pituitary tumor (Nelson syndrome). Suppression of ACTH by dexamethasone changes quantitatively (1) when observed before any therapy, (2) after bilateral adrenalectomy without evidence of a pituitary tumor or (3) in the presence of evidence of a pituitary tumor. This situation suggests a con-

tinuum rather than a change of the underlying pathology. Because we know that a pituitary tumor exists in the context of Nelson syndrome, we have reasoned that one must exist before any therapy of pituitary-dependent Cushing disease. Also supporting this idea are isolated reports of cure of Cushing disease by pituitary adenomectomy where normal pituitary adrenal dynamics return after pituitary operations.[4,7,8] For this and other reasons primary therapy often has been directed at the pituitary. Conventional pituitary radiation controls the hypercortisolism in approximately a third to a half of patients,[55] but does not seem to completely protect against the development of pituitary tumors.[54,56] Particle irradiation, however, is associated with approximately 33 percent incidence of hypopituitarism.[57,58] Radioactive yttrium or gold implantation has similar drawbacks to particle therapy in that control of hypercortisolism and tumor progression can be achieved but at the expense of a high incidence of hypopituitarism[59] and the risk of CSF rhinorrhea. The use of cyproheptadine, a serotonergic antagonist, has recently been used in treating Cushing disease. Although initially successful in some cases,[4,60] it has not been so in others.[5,61,62] The reasons for lack of universal success with this agent remain unclear. Of course, it could be possible that patients with pituitary-dependent Cushing syndrome represent a heterogeneous group of disorders, ranging from pituitary tumor to a predominantly central nervous system abnormality. Those with a predominant CNS component may be more responsive to serotonin antagonists.

It should be noted that once cyproheptadine therapy was discontinued cortisol secretion resumed at pretreatment levels in those cases where control was possible with this drug. Therefore, it should not be considered definitive therapy. Other pharmacologic agents have been tried but have serious shortcomings. The adrenocorticolytic drug (o,p′DDD or, written in full, 1-dichloro-2-[O-chlorophenyl]-2-[p-chlorophenyl]-ethane) is slow in onset, irreversibly destroys adrenocortical reserve and is poorly tolerated by the gastrointestinal tract.[63,64] Inhibition of cortisol secretion by aminoglutethimide therapy often results in exaggerated endogenous ACTH production (Cook, unpublished data) which overcomes the effect on steroidogenesis and restores cortisol secretion to pretreatment levels. Cortisol hypersecretion has been controlled with aminoglutethimide or metyrapone, or both, during or after pituitary irradiation but before full radiation effects have occurred.

Pituitary surgical procedures have been used in a surprisingly small number of cases. Hardy[65] found a small pituitary tumor in each of 10 patients. Eight of the 10 were cured, one improved and one remained unchanged. Our experience with three cases is contrary to Hardy's. In all three patients the disease persisted after transsphenoidal pituitary operations. Tyrrell and colleagues[66] have attempted transsphenoidal adenomectomy in 20 patients. In two the procedure was terminated because of large dural venous sinuses of the anterior sella. Of the remaining 18, only one did not have a pituitary tumor at the time of the operation. Sixteen of the 17 who had recognizable tumors at that time had glucocorticoids in the normal or subnormal range postoperatively. Similar transsphenoid surgical success has been reported by Schnall and associates[67] and Salassa and co-workers.[68] However, greater experience is needed with this method before it can be widely recommended. Our present therapy recommendations depend upon availability of skilled neurosurgeons and the urgency of relieving hypercortisolism. If urgency and certainty are required, bilateral adrenalectomy is still advocated. If an operation is required and skilled neurosurgeons are available pituitary adenomectomy is suggested. If the urgency is not great, we favor particle irradiation therapy if suprasellar extension does not exist. If suprasellar extension exists, then a pituitary operation is suggested followed by particle irradiation if a cure is not achieved by the surgical procedure.

The therapy for Cushing syndrome associated with adrenal adenoma is obvious. Surgical removal of the adenoma with retention of the remaining contralateral adrenal gland is the therapy of choice. The same can be said for adrenal carcinoma although, because of frequent recurrence or lack of initial surgical cure, chemotherapy is an important adjunct of the therapy.

Aminoglutethimide and o,p′DDD have been used singly or in combination. At present, there is no way to predict which agent is preferable. Frequently, o,p′DDD is not tolerated by patients because of gastrointestinal side effects of nausea and diarrhea. Although steroid values were reduced in 69 percent of 138 patients with carcinoma of the adrenal cortex, Hutter and Kayhoe were not able to show any prolongation of life in patients receiving o,p′DDD therapy.[69,70] Amino-

glutethimide has no adrenolytic properties and provides only occasional symptomatic relief.[71]

Summary

Recent advances in our understanding of the causes of hypercortisolism have been reviewed. An algorithm for differentiating these mechanisms has been proposed using techniques which have been described recently, especially quantitative plasma ACTH measurement. Interpretation of diagnostic tests requires a knowledge of their limitations. Treating patients with pituitary-dependent Cushing syndrome remains controversial —especially because the pathogenesis of this syndrome remains to be defined.

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Interim Report: National Registry of Possible Drug-induced Ocular Side Effects

THERE'S BEEN a marked increase in interest in the adverse effects of liquid high protein diets for weight reduction. Some of this interest is primarily in the area of the abnormalities shown on electrocardiograms and the cardiac complications from this type of regimen. But hyperopia . . . is a fairly common thing in these patients . . . .

—FREDERICK T. FRAUNFELDER, MD, *Portland, Oregon*

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Specialty Conference

Moderator
THOMAS T. YOSHIKAWA, MD

Discussants
NORMAN FUJITA, MD
VERITY GRINNELL, MD
JOHN E. EDWARDS, MD
ROBERT A. FELDMAN, MD

This is an edited transcript of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor-UCLA Medical Center, Torrance, California. This transcript has been edited by Thomas T. Yoshikawa, MD, and Lucien B. Guze, MD

Refer to: Yoshikawa TT, Fujita N, Grinnell V, et al: Management of central nervous system cryptococcosis—Teaching Conference, Harbor-UCLA Medical Center, Torrance, and VA Wadsworth Medical Center, Los Angeles (Specialty Conference). West J Med 132:123-133, Feb 1980

Management of Central Nervous System Cryptococcosis

THOMAS T. YOSHIKAWA, MD:* *In the past three years, our hospital has admitted several patients with central nervous system* (CNS) *cryptococcosis, whose conditions have been complicated by poor response to chemotherapy, presence of intracranial mass lesions or development of hydrocephalus. Such cases are also being seen with increased frequency by practicing physicians in our community.*

Coincident with our experience of cryptococcosis of the central nervous system has been the development of computed tomography (CT) *and the introduction of different chemotherapeutic regimens for the treatment of systemic mycoses. These newer diagnostic and therapeutic measures will have a major impact on the management of cryptococcal infections of the* CNS. *Thus, it is most appropriate to now review the current approach to the diagnosis and treatment of this fungal infection.*

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Epidemiology, Clinical Spectrum and Pathologic Findings of CNS Cryptococcosis

NORMAN FUJITA, MD:† The agent that causes cryptococcosis is a fungus, *Cryptococcus neoformans,* which belongs in the class Basidiomycetes. There are several species in the genus, *Cryptococcus;* however, only *C neoformans* is thought to be pathogenic to humans (Table 1).[1] The presence of a thick polysaccharide capsule is characteristic of *C neoformans.* However, minimal to no capsular material may also be found with this pathogen.

C neoformans has a worldwide distribution and is found in bird excreta, primarily of pigeons, and in soil, especially in areas of avian habitation. At present, four serotypes, designated A to D, are recognized, although some strains react to both anti-A and anti-D sera while others are nontypable.[2] All serotypes of *C neoformans* are believed to be equally virulent.[3]

Cryptococcosis results as a consequence of inhalation of the organism (Figure 1). The virulence and inoculum of the organism and the adequacy of host defenses are determinants of

†Fellow, Division of Infectious Diseases, Harbor-UCLA Medical Center.

ABBREVIATIONS USED IN TEXT

AB = amphotericin B
CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomography
5-FC = 5-fluorocytosine

primary pulmonary infection and subsequent dissemination. When the latter occurs, *C neoformans* invades several organ systems. For unexplained reasons, the organism has a predilection for the central nervous system. The skin and bone are less common areas of involvement and, rarely, other organs are involved.

Once infection is established in the CNS of patients, a wide spectrum of symptoms develops depending on the type and degree of involvement. The duration of symptoms before diagnosis is highly variable, but averages two to three months.[4]

Cryptococcosis of the CNS manifests as one or more of the following syndromes: chronic meningitis, encephalitis or mass lesions called cryptococcomas.

Cryptococcal Meningitis and Meningoencephalitis

Cryptococcal meningitis and meningoencephalitis occur in all races. There is an increased incidence in males, probably related to an increased outdoor exposure. Approximately 50 percent of patients have an underlying disease (Table 2). These include Hodgkin disease, non-Hodgkin lymphoma, leukemia, collagen vascular disease, sarcoidosis and diabetes mellitus. High-dose corticosteroid therapy and other immunosuppressive therapies (usually used for these previous conditions) are also important predisposing factors. All of these disease states appear to cause some defect in host response to infection.

The other 50 percent of patients with cryptococcal meningitis and meningoencephalitis have no obvious underlying disease. Recently, several groups of investigators have found subtle immunologic defects in these patients, who appear normal. Diamond and Bennett[5] have shown that lymphocytes obtained from successfully treated patients with cryptococcal meningitis had decreased transformation to heat-killed *C neoformans* when compared with lymphocytes of normal, sensitized subjects. Subsequently, Schimpff and Bennett[6] have confirmed this observation in addition to finding a decrease in leukocyte migration inhibition. These investigators have also shown decreased skin test reactivity of the "delayed-type" to common antigens as *Candida,* mumps and streptokinase-streptodornase in patients who have recovered from cryptococcal meningitis as compared with controls. Graybill and Alford[7] have shown a slight lymphocytopenia

TABLE 1.—*Species of* Cryptococcus

C albidus	*C lactativorus*
C ater	*C laurentii*
C dimennae	*C luteolus*
C flavus	*C macerans*
C gastricus	*C melibiosum*
C hungaricus	*C neoformans*
C infirmo-miniatus	*C skinneri*
C kuetzingii	*C terreus*
	C uniguttulatus

TABLE 2.—*Predisposing Conditions Associated With Cryptococcal Meningitis and Meningoencephalitis*

Hodgkin disease
Non-Hodgkin lymphoma
Leukemia
Collagen vascular disease
(systemic lupus erythematosus, rheumatoid arthritis)
Sarcoidosis
High-dose corticosteroid therapy
Other immunosuppressive therapy
Diabetes mellitus

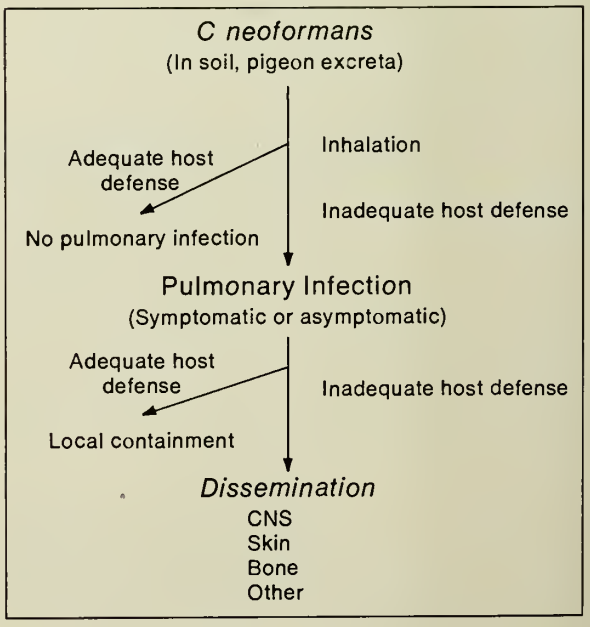

Figure 1.—Pathogenesis of cryptococcal infections. (CNS = central nervous system.)

in these patients. However, leukocyte phagocytic and fungicidal mechanisms appear to be normal.[8]

Headache is the most frequent symptom, occurring in approximately 75 percent of cases of meningitis and meningoencephalitis. Headaches are frequently localized to the frontal and temporal regions. Mental status changes occur in 50 percent of the cases and include disorientation, confusion, personality change, loss of memory, frank psychosis, stupor and coma. Eye symptoms are not uncommon and include blurred vision, diplopia, photophobia and retrobulbar pain. Nausea and vomiting are also present in a substantial number of patients, probably related to increased intracranial pressure. Pain and stiffness of the neck occur in fewer than 50 percent of cases. Other less frequently reported symptoms include ataxia, aphasia, dysarthria and seizures. Of importance is that as many as 15 percent of patients may have no symptoms referable to the nervous system and yet have infection;[4] hence, it is important to do a lumbar puncture in any patient suspected of cryptococcal infection.

On physical examination a low-grade temperature may be found. Meningismus is found in less than 50 percent of cases. Papilledema may be present. Neurologic examination may show an abnormal mental status ranging from mild confusion to coma. Cranial nerve palsies result as a consequence of increased intracranial pressure or direct nerve involvement. Hemiparesis or hemiplegia is usually associated with cryptococcomas but also has been documented in severe meningoencephalitis.[9] Cerebellar findings are also not uncommon.

On pathologic examination, cryptococcal meningitis is a chronic granulomatous meningitis which is not unlike other infectious causes of chronic meningitis. Small granulomas are usually seen within the meninges. Diffuse cortical involvement is commonly seen in autopsy specimens. The cortical disease may vary from multiple microscopic to larger macroscopic lesions.[10] On histopathologic examination, most of these lesions have little or no inflammatory response.

Cryptococcoma

Cryptococcoma is an entity that has not received much attention in the past but is now becoming well recognized and appreciated. The most recent review on this subject tabulates only 40 cases from the literature.[11] However, in our review of the English language literature (in preparation) covering the past 23 years, it is apparent that many case reports of cryptococcomas have escaped recognition by previous reviewers and, hence, this entity now appears to be more common than previously noted.

The patient population afflicted with cryptococcoma is similar to that with cryptococcal meningitis and meningoencephalitis in terms of age, race and sex distribution, but differs in that the former has a lower incidence of an associated underlying disease.[12]

Patients with cryptococcomas usually present with symptoms of focal CNS abnormalities which include hemiparesis, hemianopsia and focal seizures. If the spinal cord is involved, patients may present with quadraparesis or paraparesis. However, patients may have no localizing findings and present just with symptoms of meningitis or meningoencephalitis; the cryptococcomas are discovered incidentally.[12]

Cryptococcoma manifests as one of three basic morphologic forms: *cystic-abscess type* mass lesions,[11,13] *gelatinous* mass lesions or *fibrogranulomatous* firm mass lesions.[11,14,15] The age of the mass lesions and the nature of the host defense mechanism most likely determine the character of these lesions. Cryptococcomas may occur singly or as multiple lesions and may or may not be associated with a meningitis. They are usually found intracranially, but occasionally are found within the spinal cord or in the spinal epidural and subdural space.[11,13]

Cryptococcosis

Cryptococcosis of the CNS may be associated with other clinical findings of primary or disseminated infection. Pulmonary lesions have been associated in approximately 20 percent of cases. The classic abnormality seen on roentgenograms of the chest is an ill-defined mass lesion in the lower lung fields, usually without hilar adenopathy; other manifestations include patchy lobar infiltration and, rarely, diffuse interstitial infiltration and cavity formation.

Several skin conditions have been described and include papules, ulcers, subcutaneous nodules, abscesses and mucocutaneous lesions.

Bone involvement usually occurs in the cranial bones, vertebrae and areas of bony prominence. There may be local pain and swelling and on

roentgenographic examination, discrete, lytic lesions are seen.

Laboratory Diagnosis of Cryptococcosis of the CNS

With the exception of isolated cryptococcomas without meningeal involvement, cryptococcosis of the CNS is diagnosed by examining specimens of cerebrospinal fluid (CSF). When increased intracranial pressure is evident with papilledema, a lumbar puncture should not be done before an adequate examination for the presence of an intracranial mass lesion. Computed tomography is currently the single, best noninvasive procedure to quickly and effectively evaluate for this possibility. If a significant mass lesion is found, a neurosurgeon must be consulted to jointly formulate a diagnostic plan.

When a lumbar puncture is done, most patients with meningitis and meningoencephalitis are found to have elevated intracranial pressure (65 percent of Butler's series[4]). A lymphocytic pleocytosis with cell counts under 500 cells per cu mm of cerebrospinal fluid is present. The protein level is elevated to as high as 500 mg per dl in most patients; the level of glucose is depressed in slightly more than 50 percent of cases.

India ink preparation of the cerebrospinal fluid is positive in 50 percent of cases of meningitis,[4] and CSF cultures yield positive results in more than 90 percent of cases. Of note, *Cryptococcus* can be isolated from sites other than the CSF, and such findings can aid in diagnosis and prognosis. Cisternal punctures for fluid analysis may be helpful in undiagnosed cases of lymphocytic meningitis in which multiple lumbar punctures have not confirmed the diagnosis.[16]

In addition to the standard tests of cerebrospinal fluid, several serologic tests are available and are valuable in the diagnosis and prognosis of cryptococcal meningitis and meningoencephalitis.[17,18] The cryptococcal antigen titer can be measured in the CSF, serum and urine. The latex agglutination test is used by most laboratories to detect cryptococcal antigen. The test is carried out by incubating the test fluid with latex particles that have been coated with rabbit antibodies against *C neoformans*. If the cryptococcal polysaccharide antigen is present, the latex particles will agglutinate. Cryptococcal antigen will be positive in greater than 90 percent of culture-proved cases of cryptococcal meningitis.[19] However, the cryptococcal antigen test appears to be less specific than previously reported. False-positive results have been documented in both serum and cerebrospinal fluid; the false-positive rate has been as high as 20 percent in the CSF. Many but not all false-positive results are due to presence of rheumatoid factor.[20] The cryptococcal antigen test has been helpful in diagnosing several cases of culture-negative cryptococcal meningitis.[19]

TABLE 3.—*Factors Associated with Poor Prognosis in Patients with Cryptococcal Meningitis*

Positive india ink preparation*
High opening pressure*
Low glucose level*
Low cell count, under 20 cells per cu mm*
Positive cultures from multiple sites
No detectable serum antibody
Cryptococcal antigen titer in serum or cerebrospinal fluid equal to or greater than 1:32
Corticosteroid therapy
Lymphoreticular malignant condition

*In cerebrospinal fluid

Tests for anticryptococcal antibodies lack sensitivity and specificity and, hence, are not useful diagnostically.[17,18] However, in proven cases of cryptococcal meningitis, determination of the antibody titer has prognostic value.[21]

At present, there is no standardized skin test for routine clinical use.

A new diagnostic tool for rapid evaluation of the causative agents of lymphocytic meningitis has been reported.[22] Frequency-pulsed electron capture gas-liquid chromatography records a profile of the metabolic byproducts of the various infecting agents in cerebrospinal fluid. There appear to be characteristic patterns for each class of these organisms (for example, *Mycobacterium tuberculosis, C neoformans,* viruses and *Toxoplasma gondii).*

Once diagnosis of cryptococcal meningitis is confirmed, clinical and laboratory data should be reviewed to assess prognosis. Diamond and Bennett have tabulated various factors that are associated with poor prognosis (Table 3).[21]

In patients with CNS cryptococcosis attempts should be made to delineate the extent of central nervous system involvement. For this purpose, CT is an excellent diagnostic tool. It is our recommendation that all patients with cryptococcal infection of the central nervous system have CT done, not only to diagnose cryptococcomas but also to detect hydrocephalus. Dr. Grinnell will

discuss in more detail the use of computed tomography.

Radiographic Diagnosis of CNS Cryptococcosis

VERITY GRINNELL, MD:* All of the radiographic findings in central nervous system cryptococcosis are nonspecific.

Cerebral angiography in a patient with cryptococcal meningoencephalitis may show either no abnormalities or some smooth narrowing of arteries at the base of the brain. This reflects an arteritis associated with an inflammatory exudate in the basal cisterns. Similar arterial narrowing as seen on the angiogram is noted in other meningitides, especially tuberculosis and actinomycosis, although, generally, the arteritis associated with cryptococcal meningitis is less severe. In patients with mass lesions or cryptococcomas, the angiogram shows an avascular mass or masses without specific characteristics.[23]

Similarly, on pneumoencephalogram, a cryptococcoma will be seen simply as a mass lesion.[24] In patients with cryptococcal meningoencephalitis, the pneumoencephalogram may show no abnormalities or may disclose enlarged ventricles in cases of communicating hydrocephalus, a common complication of any basilar meningitis.

Although most of the angiographic data reviewed from the literature emphasize angiographic and pneumoencephalographic features, these procedures are now less frequently indicated in patients with CNS cryptococcosis. Most of the diagnostic features of cryptococcosis of the CNS can be ascertained by computed tomography, which is the most sensitive and least invasive neuroradiologic procedure. On CT, the visualizations of cryptococcomas are enhanced with contrast material in a homogeneous fashion, and are isodense or lucent before contrast infusion (Figures 2, 3 and 4). Some lesions may be surrounded by a small amount of edema, while others may show only a mild mass effect. However, these radiographic changes are nonspecific for any inflammatory mass. Similarly, cryptococcomas shown by radionuclide brain scanning will appear as nonspecific areas of increased uptake (Figure 5), a reflection of an alteration of the normal blood-brain barrier.

In patients with cryptococcal meningoencephalitis, CT findings may show no abnormalities despite clinical evidence of increased intracranial

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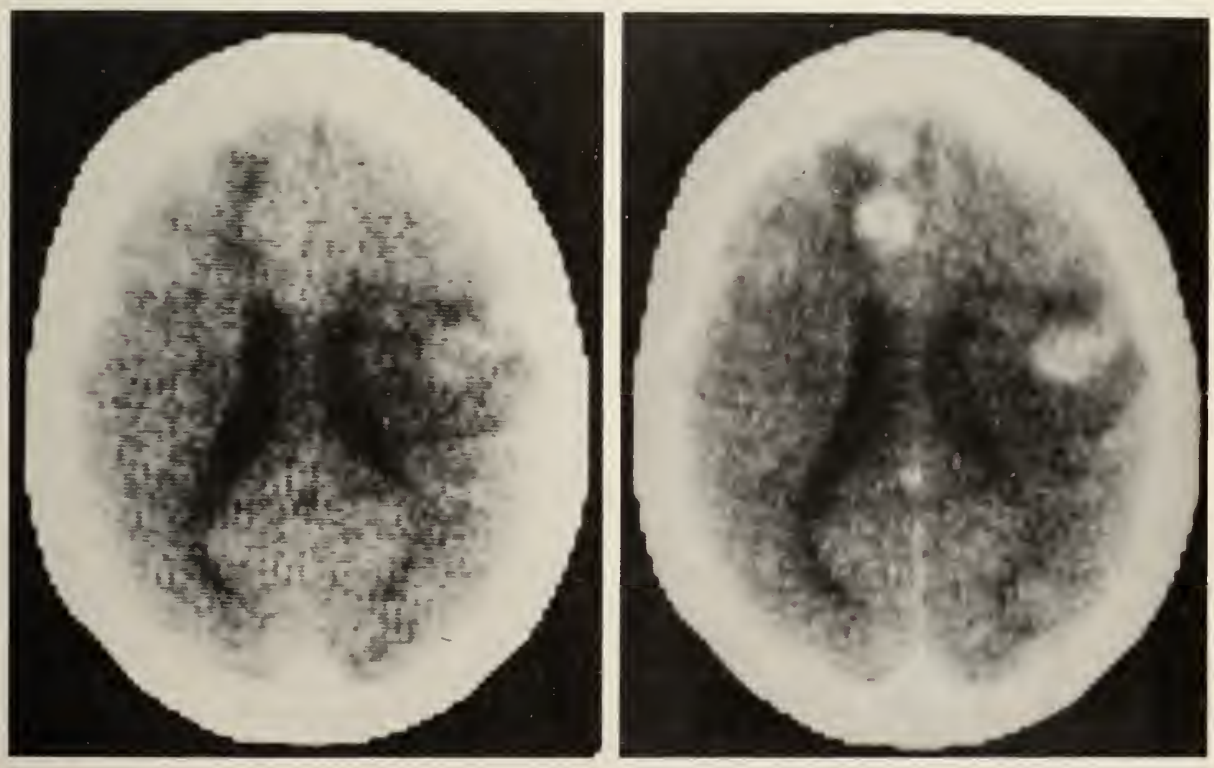

Figures 2 and 3.—Computed tomography before **(left)** and after **(right)** injection of contrast material, showing left frontal and right frontoparietal mass lesions.

pressure. Alternatively, obliteration of subarachnoid cisterns suggesting diffuse cerebral swelling may be seen. Similar findings of increased intracranial pressure, documented at ventriculostomy, without a localized mass or hydrocephalus have been reported.[15]

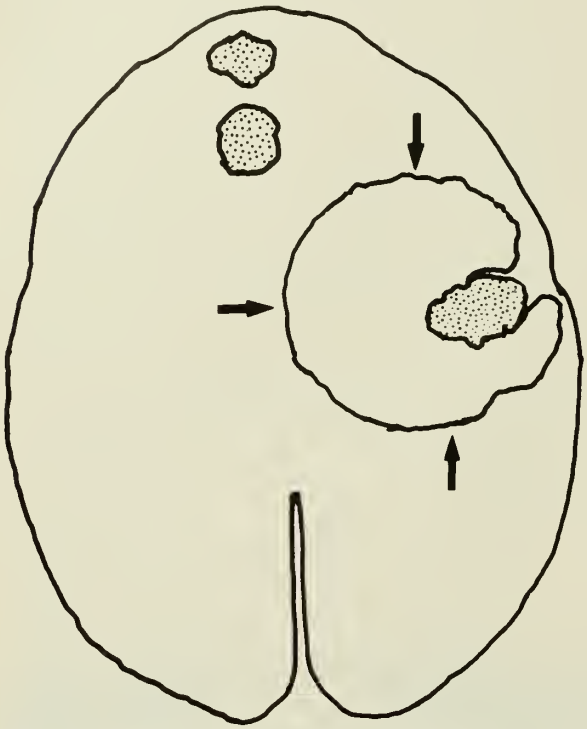

Figure 4.—Schematic drawing of Figures 2 and 3, highlighting cryptococcomas (stippled area) and "donut-shaped" area of cerebral edema surrounding the frontoparietal lesion.

Figure 5.—Findings on a technetium 99m brain scan (right lateral projection) show localized area of increased activity in the parietal area.

Chemotherapy of CNS Cryptococcosis

JOHN E. EDWARDS, MD:* The evolution of current recommendations for treating cryptococcal infection of the CNS is still continuing. I will attempt to trace chronologically the events that have led to the present chemotherapeutic approach for treating crypotococcosis.

In 1956, amphotericin B (AB) was introduced into clinical medicine. Among its applications was the management of central nervous system cryptococcosis. Before use of AB, the mortality for this infection was essentially 100 percent; using only AB, cure rates of 60 percent were reported.[21] Despite the major impact AB had on management of CNS cryptococcosis, relapses occurred in approximately one of four patients. Moreover, serious toxicities including irreversible nephrotoxicity, bone marrow suppression, thrombophlebitis, hepatic toxicity and severe discomfort during administration were common occurrences. These adverse effects occur because unlike bacteria, the fungi and yeasts are eucaryotic cells containing membrane-bound nuclei, multiple chromosomes, a mitotic apparatus, and a well-defined endoplasmic reticulum. Most pharmacologic agents which are active against these cells are also active against the cells making up human tissues.

Between 1956 and 1964, there was essentially no other effective chemotherapy available for management of cryptococcal infections other than AB. In 1964, publications began to appear regarding the possible clinical usefulness of 5-fluorocytosine (5-FC).[25] The agent was found to have activity against *Cryptococcus, Candida* and *Torulopsis,* its mechanism of action being the inhibition of protein synthesis following intracellular conversion of 5-FC to 5-fluorouracil. The advantages of 5-FC over AB included oral administration and less nephrotoxicity.

In 1971, Medoff and colleagues reported on the synergistic activity of AB and 5-FC against yeast organisms including three isolates of *Cryptococcus.*[26] The basis of this synergistic effect was thought to be increased permeability of the cell membrane by AB, which would then permit increased incorporation of 5-FC into the cell. Following the publication of Medoff and co-workers, Shadomy and associates confirmed their observation in numerous isolates of *Cryptococcus.*[27] They

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showed a synergistic fungistatic and fungicidal effect with 24 percent and 7 percent of the isolates, respectively. Three of the cryptococcal isolates responded to the combination of AB and 5-FC with an antagonistic effect.

During the time of the in vitro evaluation of the AB and 5-FC combination, clinical trials began for the treatment of various mycoses with 5-FC. In 1972, Block and Bennett treated a group of 21 patients with cryptococcal meningitis with 5-FC alone.[28] Emergence of resistance to 5-FC during therapy resulted in treatment failure in 29 percent of the patients and was considered to be a major therapeutic problem. During the study, significant toxicity developed in 38 percent of the patients. By comparison, the investigators' experience in treating 104 patients with AB at a dose of either 25 to 50 mg per day or twice that amount every other day resulted in a cure of 62 patients (only 38 percent of whom were neurologically normal). In three of these patients, final cure was attributed to supplemental intrathecal therapy. However, these cured patients received a mean total of 3.7 grams of AB. The toxicity rate and details of the types of toxicities were not described.

The lack of optimal response with either drug used alone and the in vitro studies showing synergistic activity with a combination of drugs led to clinical trials with combined AB and 5-FC. In 1975, the first prospective study using this combination was published by Utz and co-workers.[29] The objectives of the study were (1) to achieve a therapeutic response better than that realized by either drug alone; (2) to use lower doses of AB in an attempt to reduce toxicity, and (3) to treat patients for six weeks rather than ten to decrease time in hospital. Twenty consecutive patients with cryptococcal meningitis were treated. Of the 12 patients who completed their therapy, there were no relapses after a mean follow-up of 17 months. The dosages given in this study were 150 mg per kg of body weight per day of 5-FC and 20 mg per day of AB. Nine of the patients had hematologic toxicity. However, because of their underlying disorders, antifungal therapy was considered the cause in only three patients. Thrombocytopenia was the most important hematologic toxicity. Recently, Bennett and colleagues[30] reported the results of a prospective and randomized multicenter study of 78 patients with cryptococcal meningitis, 66 of whom could be evaluated for therapeutic response. AB alone was given in a dosage of 0.4 mg per kg of body weight per day for six weeks. A dosage of 0.8 mg per kg of body weight per day was then administered every other day for four weeks. The group that received the combination therapy was given 0.3 mg per kg of body weight of AB and 150 mg per kg of body weight of 5-FC each day for six weeks. Response rates of 47 percent with the AB alone and 68 percent with the combination were achieved. On the basis of this study, it was concluded that the combination form of treatment was superior to AB alone with respect to favorable response rate and number of days required for fungal suppression.

The role of intrathecal administration of AB deserves comment. The experiences of other investigators suggest that intrathecal administration of AB may not always reduce mortality or morbidity. Of 36 patients with CNS cryptococcosis treated with antifungal drugs in Butler and colleagues'[4] study, three of 12 patients (25 percent) who had intravenous and intrathecal administration of drugs died of progressive meningitis, as compared with two of 24 (8 percent) treated by the intravenous route alone. Of the patients reported by Edwards and co-workers,[31] 15 of 19 (84 percent) were cured with antifungal agents. Seven of those patients who were cured and three of those who died received intrathecal administration of medication. Diamond and Bennett, in a separate paper, reported therapeutic results of patients with cryptococcal meningitis, of whom 62 (57 percent) were cured with antifungal drugs.[32] Intrathecal instillation of drugs was not used in 77 percent (N = 48) of those cured. Of those not cured, 36 percent (N = 17) were given medications by both routes. These data indicate that intrathecal administration of medication may not improve the cure rate. However, the intrathecal route has been reserved, in almost all cases, for patients considered to have more serious disease.[4,22,31]

Clearly, many patients are curable with intravenous administration of drugs alone. Some patients, however, appear to benefit from the addition of intrathecal administration of antifungal agents. In Butler's study,[4] relapse rate appeared to be less frequent among patients who received drugs by both routes. Diamond and Bennett suggested that the intrathecal route for drugs should be considered for patients who relapse or fail to respond to a usual course of intravenous therapy, or in whom toxic effects of intravenously admin-

istered drugs preclude adequate dose levels.[32] Additionally, patients with poor prognostic factors (Table 3) may warrant intrathecal therapy. However, caution must be used in the intrathecal administration of drugs because some patients may have increased intracranial pressure.

The methods and complications of intrathecal administration of drugs will be further discussed by Dr. Feldman.

Another antifungal chemotherapeutic agent, miconazole, is now commercially available but still under clinical evaluation. It is one of several imidazole compounds having antifungal activity, and was initially reported to be effective in treating disseminated coccidioidomycosis.[33] Miconazole has less severe systemic toxicity than AB and possibly higher penetration into the cerebrospinal fluid. The major adverse effects of this drug are thrombophlebitis, hyponatremia, pruritus, nausea, vomiting, rash and febrile reaction. Unfortunately, at this time there is only limited clinical experience with the use of this agent in the treatment of CNS cryptococcosis.[33,34] It is still too premature to make a definitive recommendation regarding miconazole for treating this infection.

In summary, analysis of the literature would indicate that the treatment of choice for cryptococcal infection of the central nervous system is a combination of 5-FC and AB. Miconazole therapy requires further evaluation before definitive conclusions can be reached regarding its efficacy and complication rate. Whether patients who are severely ill at the time of their presentation and who meet the criteria for poor prognosis (Table 3) will require initial therapy with supplemental intrathecal administration of AB is controversial and cannot be definitely determined from our limited experience and review of the literature. However, it has been our usual practice to treat such patients with intrathecal instillation of AB for the initial course of their therapy, in combination with intravenous and oral administration of AB and 5-FC, respectively. When using combined therapy, patients should be monitored for hematologic and renal toxicity.

Neurosurgical Treatment of CNS Cryptococcosis

ROBERT A. FELDMAN, MD:* Although cryptococcal infection of the CNS is a relatively rare occurrence, neurosurgeons are frequently asked to participate in the care of such patients. For instance, patients with a cryptococcal infection may present with evidence of an intracranial mass; hydrocephalus may complicate cryptococcal meningitis, and intrathecal instillation of antifungal drugs may be required for seriously ill patients. Surgical intervention may be necessary in treating any or all of these facets of the disease.

Neurosurgical management of cryptococcomas generally requires standard operative intervention in patients presenting with mass effect.[35] This usually involves craniotomy with resection of the granulomatous mass. Often the diagnosis of cryptococcal disease is not established before the operation, as many patients present with no previous history or evidence of cryptococcal disease.[11] Lumbar puncture is contraindicated in the presence of signs of intracranial mass effect, but even when cerebrospinal fluid is obtained, definitive evidence of the cryptococcal disease is not always seen.[31,35] Similarly, pathognomonic characteristics of cryptococcoma have not been identified with either plain x-ray or special radiographic techniques (see Dr. Grinnell's discussion). The anticipated role of surgical operations, therefore, may be diagnostic as well as therapeutic. In a review of the literature, Selby and Lopes[11] compiled studies of 40 patients with cryptococcal granuloma, all of whom underwent surgical excision of the mass. Only 36 percent of the patients survived to follow-up (1 month to 21 years). However, some of these patients underwent surgical excision of their cryptococcomas before the introduction of amphotericin B in 1956 and at the time when cryptococcal involvement of the CNS was considered uniformly fatal.[31,32,36] Two of three patients from Selby and Lopes' own series survived after surgical treatment and use of antifungal agents.[11] Combining antifungal drug therapy with or after operations has been considered imperative for cryptococcomas because (1) the resected mass may be the only conspicuous abnormality in the presence of many other cryptococcal lesions; (2) accidental spillage of organisms may occur during the procedure, and (3) negative CSF findings are known to occur in the presence of active cryptococcal disease.

Hydrocephalus also requires neurosurgical consideration and is a well-recognized complication of cryptococcal meningitis. Hydrocephalus in cryptococcosis may be a communicating type[35] resulting from a restriction of cerebrospinal fluid

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pathways in the basal subarachnoid space due to inflammation. Shunting of ventricular cerebrospinal fluid was required because of hydrocephalus in nine of 21 patients in the Diamond and Bennett study[32] and in 15 of 30 patients in the study by Richardson and co-workers.[35] When signs of hydrocephalus (confusion and lethargy are the most prominent) correlate with radiographic findings of an enlarged ventricular system, improvement of a patient's mental status is often seen after insertion of a device to divert CSF.[35]

Neurosurgical assistance for intrathecal instillation of antifungal drugs is sometimes requested for complicated cases of CNS cryptococcosis. Insertion of a subcutaneous (Ommaya) reservoir[32,37] with a catheter placed into the lateral ventricle is convenient for access to intracranial cerebrospinal fluid to (1) instill antifungal drugs; (2) obtain CSF for analysis; (3) measure intracranial pressure, and (4) remove excess cerebrospinal fluid in patients in whom hydrocephalus is developing.

It would appear from the foregoing comments that neurosurgical participation in the treatment of patients with CNS cryptococcosis is straightforward. Unfortunately, however, several aspects of the neurosurgical treatment of this condition are not well delineated, often raising questions as to the proper management for individual patients. Although clear answers are frequently not available, questions often asked include the following.

- *Is lumbar puncture or subcutaneous (Ommaya) reservoir preferred for intrathecal instillation of antifungal drugs?*

Richardson and co-workers claim that lumbar puncture is safe in patients with cryptococcal meningitis because increased intracranial pressure is due to communicating hydrocephalus.[35] However, this assumption fails to account for patients with raised intracranial pressure due to a focal mass lesion or generalized cerebritis, both of which can occur with cryptococcal infection of the CNS.[14] Doing a lumbar puncture under these circumstances increases the risk of tentorial or cerebellar herniation. Ommaya claims that the distribution of drugs in CNS pathways is better when the agent is introduced into the ventricles as compared with the lumbar theca.[38] On the other hand, Rieselbach and colleagues[39] showed that distribution of drugs after lumbar injection was largely dependent on volume, and that significant drug concentrations were seen in the basal cisterns if 10 percent or more of the calculated CSF volume was injected. However, in a disease state such as hydrocephalus or meningeal inflammation, cerebrospinal fluid dynamics may be altered. Moreover, lumbar puncture in certain patients may be impractical. For instance, adhesive arachnoiditis may develop after multiple injections of antifungal drugs.[37] A radioisotope cisternogram may be used if patency of the cerebrospinal fluid pathways is in question.[40]

The Ommaya reservoir is usually easy to insert and simple to use. Because it drains into the large ventricular fluid volume, irritation of membranes from instilled medications is less likely than in the lumbar space. The risk of cerebellar herniation is precluded with the Ommaya reservoir. However, the reservoir is not without hazards.[32,41] Diamond and Bennett reported on 21 patients with cryptococcal meningitis, in whom a total of 31 Ommaya reservoirs were inserted.[32] There were 47 complications related either to the insertion or use of the reservoirs. Based on autopsy information, reservoir insertion was felt to be a major contributing cause of death in three patients. CSF infection was the single most common (N = 8) complication. The need emphasized by Tobias and co-workers[36] for high intraventricular concentrations of medication offered by the Ommaya reservoir is not well substantiated for CNS cryptococcal infections. The disease involves primarily the subarachnoid cerebrospinal fluid pathway,[42] and only two cases of intraventricular cryptococcal granuloma have ever been reported.[43,44]

- *How should bacterial infections of the cerebrospinal fluid be treated in the presence of an Ommaya reservoir?*

Bacterial infection of the CSF in the Ommaya reservoir, with or without colonization of the generalized cerebrospinal fluid pathways, is a common complication[32,41] and probably represents, in most cases, contamination by skin bacteria.[41] Generally, surgeons advocate immediate removal of the reservoir should colonization occur.[37,41] However, Diamond and Bennett cite four cases in which antibiotics alone were used for successful clearing of bacterial infections and preservation of functioning reservoirs.[32]

- *Is ventricular fluid more likely to yield evidence of cryptococcal infection than lumbar spinal fluid?*

Edwards and colleagues[31] suggest, whereas

Richardson and co-workers[35] deny, that ventricular fluid will yield positive evidence of cryptococcal infection more frequently than lumbar spinal fluid. Evidence supporting either of these statements is not well documented.

• *Does ventricular shunting affect the course or treatment of cryptococcal infection of the central nervous system?*

As mentioned earlier, ventricular shunting has been shown to effectively treat signs and symptoms related to hydrocephalus associated with central nervous system cryptococcosis. However, shunting, be it ventriculoatrial or ventriculoperitoneal, is not without hazard. The incidence of bacterial infection related to shunt insertion or revision is approximately 15 percent to 20 percent.[45,46] Other complications, such as mechanical shunt failure, worsening of neurological status associated with insertion and abdominal viscus perforation, occur less frequently. Shunt systems may cause obstructions when used in patients with elevations of CSF protein.[47] Such elevations may occur in cryptococcal meningitis and may require the use of specially designed shunt systems.[47] Cerebrospinal fluid concentrations of intrathecally administered antifungal drugs are poorly maintained in the presence of a functioning shunt,[32] though further development of shunt valves with on-off mechanisms[48] may obviate this potential problem. Concern that ventricular shunting will spread cryptococcal infection to the blood stream or peritoneal cavity appears unwarranted.[35]

Alternatives to shunting in the presence of symptomatic hydrocephalus are limited. Serial spinal or Ommaya reservoir taps may relieve CSF pressure long enough for the inflammatory reaction to subside and for normal cerebrospinal fluid circulation and reabsorption to resume.

• *Should smaller, asymptomatic cryptococcal granulomas, which are sometimes multiple, be removed?*

Granulomas may be mutiple,[15] arousing suspicion of metastatic lesions, particularly in the absence of meningeal signs. For this and other reasons, diagnostic considerations may determine the need for a surgical operation. In addition, there is evidence that cryptococcal organisms can remain viable in a granuloma even after adequate antifungal therapy.[15,49] Brisman and colleagues suggested that persistence of organisms might be due to the avascular nature of the granuloma which could limit adequate drug concentrations to the center of the lesion.[49]

The questions that have been discussed above are those that most commonly arise concerning neurosurgical participation in the treatment of patients with central nervous system cryptococcosis. Other questions may also arise as individual clinical situations occur. Although some facets of the neurosurgical management of patients with cryptococcal infections of the CNS are dictated by clearly defined guidelines, many other aspects are not yet well established.

Summary

DR. YOSHIKAWA: *From the discussion presented by our speakers, the following points regarding cryptococcosis are worth reemphasizing.*

• *Central nervous system cryptococcosis may occur as meningitis, meningoencephalitis or a mass lesion or lesions.*

• *Diagnostic evaluation of any patient with cryptococcal infection should include computed tomography.*

• *Current chemotherapy of choice is a combination of amphotericin* B *and 5-fluorocytosine.*

• *The role of supplemental intrathecal therapy for central nervous system cryptococcosis is not clearly defined at present.*

• *Cryptococcal mass lesions should be surgically excised if technically feasible.*

• *Hydrocephalus should be managed by shunting procedures.*

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Tubulo-interstitial Nephropathies—A Pathophysiologic Approach

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

DR. SCHMID: **This grand rounds' presentation will focus on interstitial renal disease. Dr. Martin Cogan from the Division of Nephrology is the discussant.*

DR. COGAN:† Interstitial diseases of the kidney have assumed increased importance for internists as three facts have emerged in recent years. First, it has been estimated that as many as a third of all patients with end-stage renal disease have a primary chronic interstitial process as a major pathologic factor in their loss of renal function.[1] As the complexity and cost of caring for patients with end-stage renal disease continue to escalate, it would behoove us to augment our efforts to identify and treat these chronic interstitial diseases. This is especially important because many types of interstitial kidney disease, such as analgesic abuse nephropathy, are preventable. Second, as opposed to glomerulonephritis, it is now firmly established that many forms of interstitial nephritis can be easily and quickly treated. Compared with the controversy surrounding the efficacy of various treatment programs for lupus or membranous glomerulonephritis, there is no doubt that many forms of interstitial nephritis can be dramatically reversed by corticosteroid therapy or by simply removing an offending toxic or immunologic agent. Third, there has been an increasing awareness that particular acid-base and electrolyte disorders accompany interstitial but not glomerular diseases of the kidney. Such tubular dysfunction seems inevitable if one looks at the pathologic features—interstitial involvement of the kidney almost always involves pronounced tubular destruction. Conversely, a primary tubular insult can evoke an interstitial inflammatory response. Because of this close pathologic and physiologic association, I prefer the somewhat more cumbersome term of tubulo-interstitial nephropathy, to emphasize the functional (tubular) aspects of the disease process.

In this review, we will consider the general immunologic mechanisms mediating injury in the tubulo-interstitial nephropathies. We will then move briefly through a summary of the specific acute and chronic tubulo-interstitial nephropathies. Finally, before emphasizing the treatment aspects, we will concentrate on the various fluid, acid-base and electrolyte abnormalities that characterize these disorders and propose a new classification system based on these pathophysiologic

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ABBREVIATIONS USED IN TEXT
GFR = glomerular filtration rate
RTA = renal tubular acidosis

features. Recognition that such electrolyte derangements exist may be the tip-off that a renal disease, specifically a tubulo-interstitial nephropathy, is present. On the other hand, if the diagnosis of a tubulo-interstitial nephropathy has already been made clinically or by biopsy, one should be on the lookout for such electrolyte disorders so that treatment can begin before the patient is in jeopardy.

Immunologic Pathogenesis

Most tubulo-interstitial nephropathies have as a pathogenetic basis one of two fundamental immunologic mechanisms. In both, immunoglobulin deposition evokes cellular infiltration of the kidney parenchyma, with lymphocytes, monocytes and eosinophils. Some of these cells, especially eosinophils, find their way into tubule lumens and can be recovered in the urine. Examination of urine specimens for eosinophils should always be done in cases of suspected tubulo-interstitial nephropathy. Fever and rash likewise are commonly part of the allergic response.

The two forms of immunologic process that cause tubulo-interstitial disease are very similar to the immunologic processes that cause glomerulonephritis: (1) direct attack of antibodies against the basement membrane and (2) deposition of antigen-antibody complexes near basement membranes.[2-4]

The first type is the antitubular basement membrane form. If the immunoglobulins were to be directed against pulmonary or glomerular basement membranes, Goodpasture disease would ensue. Instead, the immunoglobulins, especially IgG, are formed against renal tubular basement membranes. The prototype for this process is methicillin-induced tubulo-interstitial nephropathy.[5] In this case, antibodies are formed against part of the methicillin molecule, the dimethoxyphenyl penicilloyl moiety. These antibodies then cross-react with the renal tubule basement membrane and evoke a round cell infiltration. A linear immunofluorescent pattern is observed. Specific attack on either proximal or distal tubule basement membranes has been described.

The second type of immunologic injury can be evoked if an antigen combines with antibody and then becomes deposited alongside the renal basement membrane.[2-4] This is the tubulo-interstitial equivalent of some forms of glomerulonephritis.

TABLE 1.—*Causes of Tubulo-interstitial Nephropathies*

ACUTE TUBULO-INTERSTITIAL NEPHRITIDES

- Associated with drugs:
  - Methicillin
  - Penicillin and derivatives
  - Cephalosporins
  - Sulfa derivatives
  - Antitubercular drugs
  - Antiepileptic drugs
  - Allopurinol
  - Phenacetin
- Associated with immunologic diseases:
  - Transplant rejection
  - Sjögren syndrome
  - Lupus
- Idiopathic
- Associated with infection:
  - Bacterial
  - Granulomatous
    - Tuberculosis and leprosy
    - Sarcoid
    - Leptospirosis
    - Toxoplasmosis
    - Syphilis
    - Mycetoma
  - Viral (especially mononucleosis)
- Secondary to interstitial inflammation:
  - Pyelonephritis
  - Acute tubular necrosis
  - Toxic
- Secondary to primary glomerular disease or vasculitis

CHRONIC TUBULO-INTERSTITIAL NEPHROPATHIES

- Metabolic
  - Hypercalcemia
  - Hyperuricemia
  - Sickle cell
  - Paroxysmal nocturnal hemoglobinuria
  - Hyperoxaluria
- Neoplastic
  - Multiple myeloma
  - Leukemia
  - Lymphoma
- Immunologic
  - Sjögren syndrome
  - Lupus
  - Transplant rejection
- Toxic
  - Analgesic
  - Balkan
- Hereditary
  - Polycystic
  - Medullary cystic

In those kinds of glomerulonephritis, an immunofluorescent pattern of granular immune complex deposition occurs, such as in poststreptococcal, membranous or lupus glomerulonephritis. When such immune complexes are deposited by unknown determinants in the interstitium rather than in the glomerulus, a monocellular infiltration arises. The prototype of this form of tubulo-interstitial nephropathy is lupus, in which proximal and distal basement membrane immune complex deposition can uncommonly be as severe as in the glomerulus.[6]

Causes

With this brief background for the immunological basis of tubulo-interstitial nephropathies, let us examine some of the agents that provoke such a response. Because tubulo-interstitial nephropathies may be either acute or chronic, we will separate them and consider the acute forms first. *Acute tubulo-interstitial nephritis* usually occurs from one to three weeks after an agent is introduced.[7-9] It is characterized by a decrease in glomerular filtration rate (GFR) that may be mild to severe. Typically, if the process is mild and slower, the patient will be nonoliguric. If the process is more rapid, the GFR will decline quickly, the patient will be oliguric, and the acute renal failure may have to be treated with dialysis. Processes that can evoke acute interstitial nephritis are listed in Table 1[7,9] and basically can be divided into those associated with drug administration, immunologic disorders, an idiopathic form, infections, inflammatory processes, and those secondary to other renal or vasculitic processes. The most common of these is the tubulo-interstitial nephritis caused by penicillin and its derivatives, especially methicillin.[5,10,11] With acute methicillin tubulo-interstitial nephritis there are frequently associated eosinophilia, sterile pyuria, hematuria, fever and rash that occur due to the allergic response to the drug. A recrudescence of fever after an infection has been treated, associated with a decline in renal function, can be a sign that a drug reaction is occurring.

To summarize, the typical clinical features in a patient with acute tubulo-interstitial nephropathy are the development, after a week or two of drug treatment or in association with an infection or collagen disease, of oliguric or nonoliguric acute renal failure along with a fever, rash, eosinophilia and sterile pyuria with hematuria. There are never red cell casts and only minimal proteinuria, however; both of these are markers of glomerulonephritis, not tubulo-interstitial nephritis.

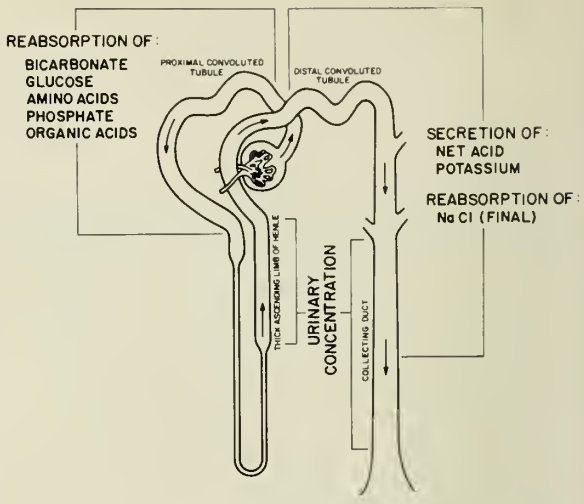

Figure 1.—Segmental physiologic aspects of nephron function. Schematically represented are the principal nephron segments and transport properties that can be individually affected by tubulo-interstitial nephropathies: the proximal nephron, which reabsorbs the bulk of bicarbonate, glucose, amino acids, phosphate and organic acids following glomerular filtration; the distal nephron, which is responsible for reabsorbing the final quantity of luminal sodium, for secreting hydrogen ions to generate net acid excretion as well as for secreting potassium; and the medullary and papillary structures, the loops of Henle and collecting ducts, which abstract water to concentrate the urine.

The presentation of patients with *chronic tubulo-interstitial nephropathy,* on the other hand, does not usually include the pronounced allergic features seen in the acute form. The various metabolic, neoplastic, immunologic, toxic and hereditary causes of chronic interstitial nephritis are shown in Table 1.[1,7] They lead to slowly progressive renal insufficiency that is indistinguishable from chronic glomerulonephritis except that normotension is more commonly present and except for some of the electrolyte abnormalities discussed later. Of particular importance in this group of disorders, however, is the recent recognition that chronic analgesic abuse can cause progressive renal interstitial damage that can potentially lead to an end-stage condition.[1] Phenacetin is usually present in the ingested analgesic combinations, but need not be. Withdrawal of analgesic drugs can halt the renal damage. The older conception that chronic infections are a common cause of chronic tubulo-interstitial disease has yielded to the notion that only infections associated with obstructive processes of the

urinary tract cause chronic damage. The diagnosis of chronic pyelonephritis as a cause of significant renal dysfunction should be reserved only for these unusual conditions associated with chronic obstruction. More specific metabolic or toxic causes of a chronic interstitial process must be sought, rather than assuming an unidentified chronic infectious condition exists.

Pathophysiologic Features

Having briefly surveyed the clinical spectrum of acute and chronic tubulo-interstitial nephropathies, let us turn to some of the functional consequences associated with them. Although a decrease in glomerular filtration rate commonly occurs in these diseases, there are frequently electrolyte disturbances that are disproportionately severe for the level of GFR reduction. I will approach these disorders according to nephron geography; that is, according to which segment of the nephron is more seriously affected.

There are two purposes for the physiologic classification of these diseases. First, attention is called to the disease-specific acid-base and electrolyte derangements that can aid in diagnosis or call for therapy after a diagnosis has been reached. Second, it is hoped that the grouping of diseases in this way will stimulate the search for the pathogenetic factors that make the destruction of a single nephron segment so selective and so prominent.

The functional abnormalities can be divided into those that are caused primarily by disruption of proximal nephron function, distal nephron function, and loop of Henle and collecting duct function as illustrated in Figure 1. This categorization clearly is oversimplified because more than one segment may be involved. Also, renal physiologists are increasingly aware of functional subdivisions of nephron segments. For instance, there are now recognized to be three distinct subsegments of the proximal tubule and at least three morphologic subsegments of the distal tubule. Nevertheless, a first approximation of the important functional aspects of the tubulo-interstitial nephropathies can be gained when the electrolyte dysfunctions are ordered in this way. A concise diagnostic and therapeutic classification system emerges.

There are some interstitial processes that affect almost exclusively the *proximal nephron,* either by cellular infiltration or by glomerular filtration of presumably toxic substances. The proximal tubule is responsible for 80 percent of the total renal bicarbonate reabsorption. Bicarbonate reabsorption is accomplished by hydrogen ion secretion accompanied by sodium reabsorption. Other sodium co-transported solutes reabsorbed in the proximal nephron include glucose, amino acids, phosphate and organic anions, including uric acid (Figure 1). Therefore, a patient with a tubulo-interstitial nephropathy that affects the proximal tubule will have the bicarbonate-wasting or proximal form of renal tubular acidosis (RTA) and inappropriate glycosuria, amino aciduria, phosphaturia and uricosuria, together known as the Fanconi syndrome.

TABLE 2.—*Patterns of Renal Dysfunction in Tubulo-interstitial Nephropathies: Primarily Affecting Proximal Tubule**

Multiple myeloma (± distal)
Paroxysmal nocturnal hemoglobinuria
Heavy metals
? Antitubular basement membrane idiopathic tubulo-interstitial nephritis
? Lupus
? Acute myelogenous leukemia

*Proximal RTA with or without Fanconi syndrome.

As seen in Table 2, a patient with the proximal form of RTA with or without the Fanconi syndrome must be considered to have multiple myeloma until proved otherwise.[12] Other tubulo-interstitial nephropathies responsible for this syndrome include paroxysmal nocturnal hemoglobinuria,[13] heavy metals[14,15] and, less well documented, an antitubular basement membrane idiopathic form,[8,16] lupus,[7] and acute myelogenous and myelomonocytic leukemic[17] forms of tubulo-interstitial nephropathy. It should be mentioned that in caring for a patient with multiple myeloma, the development of proximal RTA or the Fanconi syndrome should be considered in the spectrum of myeloma renal disease.

The *distal nephron* is mainly concerned with the regulation and conservation of the final quality of sodium in the tubular fluid and the secretion of potassium and hydrogen ions (Figure 1). The hydrogen ions titrate the small amount of bicarbonate escaping proximal reabsorption, lower the urinary pH, and titrate ammonia and other buffers to effect urinary net acid excretion. A defect in distal nephron function will result, therefore, in the distal form of renal tubular acidosis characterized by high urinary pH, with or without clinical salt wasting or hyperkalemia.

There are numerous examples of the selective

disruption of distal nephron function sometimes accompanied by a defect in urinary concentrating ability but with normal proximal tubule function. As seen in Table 3, these disorders include amyloidosis,[18] methicillin,[19] states with hypercalcemia or nephrocalcinosis (or both),[20,21] medullary cystic disease,[22] hypergammaglobulinemic states (especially the Sjögren syndrome),[23] chronic obstructive uropathy,[24] renal transplantation,[25] granulomatous infections[26] and Balkan nephropathy.[27]

An example of how the mononuclear cell infiltrate of the kidney can selectively affect distal tubules is seen in Figure 2, which shows a renal biopsy specimen from a patient with methicillin tubulo-interstitial nephropathy.[19] Here the glomeruli and the proximal tubules are well preserved, but the distal tubules (arrows) have been invaded.

TABLE 3.—*Patterns of Renal Dysfunction in Tubulo-interstitial Nephropathies: Primarily Affecting Distal Tubule**

Amyloid
Methicillin
Hypercalcemic/nephrocalcinosis states
Primary hyperparathyroidism
Milk alkali syndrome
Idiopathic hypercalciuria
Medullary cystic disease
Hypergammaglobulinemic states
Sjögren syndrome (± proximal)
Chronic active hepatitis
Lupus
Chronic obstructive uropathy
Renal transplantation (± proximal)
Granulomatous infections
Balkan

*(Distal renal tubular acidosis ± salt wasting ± elevated potassium levels) ± collecting duct dysfunction (decreased concentrating ability).

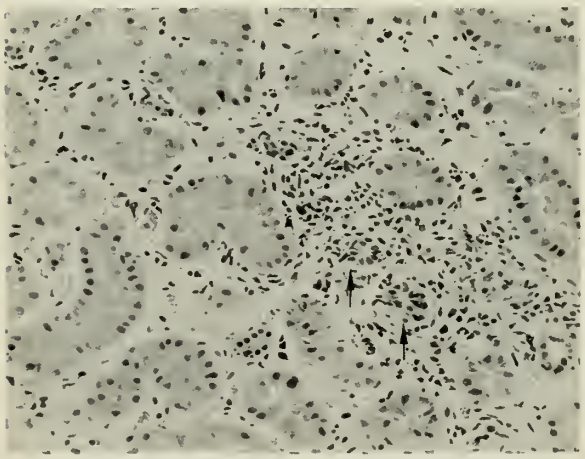

Figure 2.—Photomicrograph of a renal biopsy specimen from a patient with methicillin tubulo-interstitial nephropathy. Glomerulus (not shown) and proximal tubules are relatively spared but distal tubules (arrows) are surrounded by dense mononuclear infiltration. Reduced from original ×80. (Reproduced with permission from Cogan MG and Am J Med.[19])

As illustrated in Figure 3, this patient presented clinically with azotemia without oliguria, accompanied by dehydration, acidosis and hyperkalemia.[19] The elevated blood urea nitrogen (BUN) and creatinine could be appreciably lowered when salt was given back (period I). The hyperkalemia and acidosis were corrected as well, but after correction of the salt depletion, acidosis and hyperkalemia these electrolyte disturbances recurred when a low salt diet was instituted (period II). Salt wasting was shown to be present. Proximal nephron function was intact.

Intermediate forms of distal nephron damage by tubulo-interstitial nephropathies also exist in which normal dietary acid, potassium and salt loads are tolerated. However, stressful situations from acid-loading,[20,21] potassium loading[28] or salt restriction[29] cannot be normally handled by the kidney. Such tubulo-interstitial nephropathies can thus be categorized as displaying incomplete renal tubular acidosis, potassium intolerance or subclinical salt wasting.

In summary, the presentation of a patient with dehydration due to renal salt wasting or with hyperkalemia and acidosis disproportionate to the degree of renal insufficiency should alert one to the possibility of this distal nephron group of tubulo-interstitial nephropathies being present. Conversely, in a patient with these disorders follow-up studies should be done to check for the possible development of overt salt wasting, acidosis or hyperkalemia. Concurrent or isolated hypoaldosteronism can mimic these disorders and should also be sought because therapy differs. In the tubulo-interstitial nephropathies that affect the distal nephron, there is aldosterone resistance (period IV in Figure 3) so that renin and aldosterone levels are high. On the other hand, in the primary or the secondary (hyporeninemic) forms of hypoaldosteronism, aldosterone levels are low.

Finally, there are many diseases that primarily involve the medulla and papilla of the kidney and, therefore, disproportionately affect the *loops of Henle* and the *collecting ducts* (Figure 1). These medullary structures are responsible for water conservation. The ascending limb of Henle generates steep solute gradients in the interstitium using the countercurrent multiplication system.

The collecting ducts allow water to flow out of the tubule lumen when antidiuretic hormone is present. Disruption of these structures can lead, therefore, to polyuria due to mild nephrogenic diabetes insipidus, which occasionally can be severe.

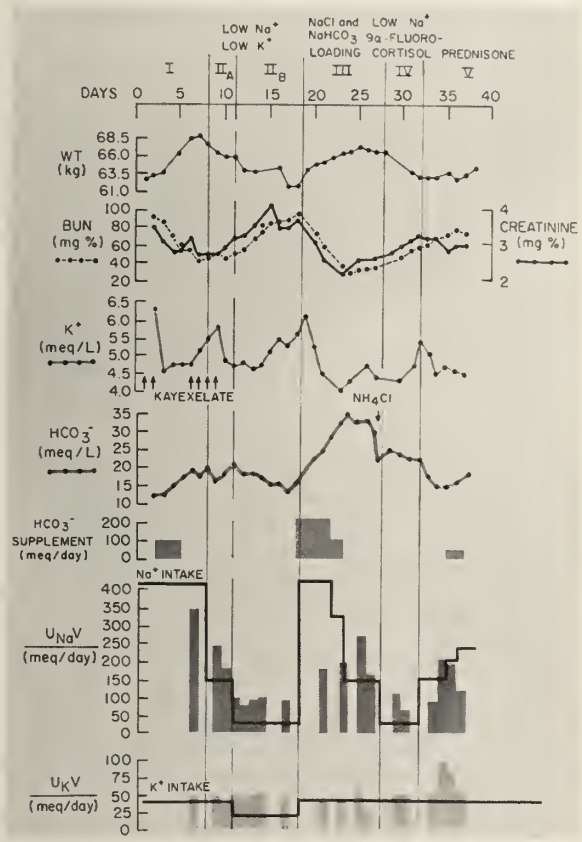

Figure 3.—Metabolic testing of a patient with methicillin acute tubulo-interstitial nephropathy (renal biopsy specimen is shown in Figure 2). The weight loss, azotemia, hyperkalemia and metabolic acidosis on admission were repaired in period I, but recurred during salt restriction in period II accompanied by pronounced renal salt wasting. The response to salt and bicarbonate loading, mineralocorticoid and prednisone administration are shown in periods III to V. See text for further discussion. (Reproduced with permission from Cogan MG and Am J Med.[19])

TABLE 4.—*Patterns of Renal Dysfunction in Tubulo-interstitial Nephropathies: Primarily Affecting Medullary Structures**

Drugs: analgesic nephropathy
Acute pyelonephritis
Sickle cell disease (± distal)
Hyperuricemic and hyperoxaluric obstructive nephropathies (± distal)
Medullary sponge kidney (± distal)
Polycystic kidney disease (± distal)
Sarcoidosis
? Hypokalemic nephropathy

*Decreased concentrating ability.

TABLE 5.—*Clinical Tip-offs That Renal Failure Is Due to Interstitial Rather Than Glomerular Process*

General
- History of drug exposure (especially penicillin derivatives)
- Fever, rash

Blood
- Normal blood pressure
- Eosinophilia
- "Inappropriate" acidosis and hyperkalemia

Urine
- Normal urine output
- Nonspecific sediment (no red blood cell casts); pyuria and eosinophiluria
- Mild ("tubular") proteinuria
- Isosthenuria; high urine pH; glycosuria or amino aciduria (Fanconi)

A partial list of the tubulo-interstitial nephropathies mainly affecting the medulla and papilla of the kidney and consequently impairing water conservation is given in Table 4. These include analgesic nephropathy,[7] acute pyelonephritis,[30] sickle cell disease,[31] hyperuricemic and hyperoxaluric obstructive nephropathies,[32] medullary sponge and polycystic kidney diseases,[33] sarcoidosis,[34] and perhaps hypokalemic nephropathy.[35]

These diseases have a predilection for the papilla and medulla more because of the physicochemical properties of this area of the kidney, being relatively hypertonic and anaerobic, rather than due to immunologic properties. Proximal and distal nephron functions are usually intact, however.

To summarize the immunologic basis for the tubulo-intersitial nephropathies and to emphasize some of the electrolyte abnormalities that are peculiar to them, it is useful to review the characteristics of acute interstitial processes that distinguish them from glomerular processes (Table 5). The allergic basis for many acute tubulo-interstitial nephropathies suggests that fever, rash and eosinophilia may exist. The disproportionate effect on tubules, rather than on the glomerular filtration rate, means that a patient may be normotensive, nonoliguric, and acidotic or hyperkalemic out of proportion to the degree of renal insufficiency present. The urine is also more likely to contain white cells, and especially eosinophils, but not red cell casts or heavy proteinuria. When these features are present, an astute internist can make a presumptive diagnosis of a tubulo-

interstitial nephropathy. Of course, a renal biopsy is necessary for definitive description.

Treatment

The diagnosis of a tubulo-interstitial nephropathy is of more than academic concern because many types are treatable. If a drug is at fault in acute cases, simple withdrawal of the drug is usually sufficient to halt the renal damage. The prognosis is excellent for full return of renal function. The treatment of an underlying infection or collagen vascular disease also causes the renal interstitial disease to abate. In chronic tubulo-interstitial nephropathies, treatment of the underlying disease is often sufficient to cause regression of the renal lesion. It is very important to question patients closely about analgesic consumption because cessation of drug ingestion will halt the renal damage.

Prednisone acts promptly to accelerate the healing process in moderate doses, such as 1 mg per kg of body weight.[10] In general, treatment should not be attempted unless the renal pathologic condition is known from biopsy results. However, if clinical suspicion is high enough because of the historical, immunologic and functional characteristics we have discussed, and if the patient is too ill to tolerate a biopsy safely, I think a brief course of steroids can be recommended. The response is usually observed quickly, within a week, before chronic adverse effects of the steroids become evident.

In conclusion, I hope this emphasis on the pathophysiologic characteristics of the tubulo-interstitial nephropathies, in conjunction with the immunologic and treatment aspects, has served to heighten awareness and stimulate interest in this group of diseases. Certainly, the interrelationships of structure and function are nowhere more elegantly exemplified in nephrology than in these disorders.

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Important Advances in Clinical Medicine

Epitomes of Progress—Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in neurology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Lumbar Puncture and Febrile Seizures in Small Infants

SMALL INFANTS with fever who have a focal or generalized seizure represent a special problem for clinicians. Between three months and four years of life, the normal child has an increased incidence of febrile seizures. Assessment of young infants for meningitis is difficult since they may fail to have clinical signs of meningeal irritation. In very young infants diffuse lesions may result in focal seizures; focal lesions may result in generalized seizures.

The problem of diagnosis of meningitis in small infants with seizures is illustrated in two studies. Routine lumbar puncture in 314 infants presenting with their first febrile seizure disclosed four cases of unsuspected meningitis. One 12-month-old infant had meningitis due to *Hemophilus influenzae* and three infants, all less than 16 months of age, had meningitis from a viral or a presumed viral cause. In two additional cases with normal findings on initial cerebrospinal fluid studies, repeat lumbar punctures were done two days later and showed meningococcal meningitis.

In another study, in 11 of 27 patients with a first febrile seizure in association with meningitis, no clinical signs of meningitis were seen. All were less than 16 months old. Four of the 11 had other infections which provided an alternate explanation for the fever. In both studies, children older than 16 months with meningitis had clinical signs of the disease.

Children younger than 16 months who have febrile seizures should have cerebrospinal fluid examinations to rule out central nervous system infections because clinical signs of meningitis may be absent. Infants with prolonged increased intracranial pressure as manifested by papilledema or separation of the cranial sutures should be promptly evaluated, if possible by computerized axial tomography, before lumbar puncture to minimize risks of brain herniation.

MARVIN L. WEIL, MD

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Lioresal

LIORESAL (baclofen) is Ciba-Geigy's antispasticity agent 4-amino-3-(*p*-chlorphenyl) butyric acid. The drug appears to affect reflex pathways in the spinal cord. It is most useful for the symptomatic reduction of clonus, muscle tightness and aching, "jumping of legs" at night, and flexor or extensor spasms (such as during transfers from wheelchair to bed) arising from spinal cord damage due to trauma or multiple sclerosis (MS). It has little efficacy for spasticity of cerebral origin and induces more adverse effects in older patients compared with youths. It is not a curative drug for multiple sclerosis.

Adverse clinical effects are (in order of frequency of occurrence) drowsiness which usually occurs during initiation of therapy, dizziness, increased weakness, nausea, fatigue, headache, insomnia and possibly increased constipation. Since many of these symptoms are also associated with underlying disease process (multiple sclerosis, for example) caution must be exercised in attributing adverse reactions to the drug. Gradual withdrawal and subsequent reinstitution of the drug may be necessary to show cause and effect. Interaction with sedatives and alcohol occurs. The agent is not approved for use in children or pregnant or lactating women. The product insert (prescribing information) suggests starting dosage at 5 mg three times a day for three days, then gradually increasing to 20 mg three times a day. I often start at 5 mg given at bedtime for three to five days and then gradually increase the dosage. Some patients with MS seem exquisitely sensitive to the drug. Also starting with a dose given at bedtime significantly decreases complaints of drowsiness.

Close supervision of the patient is necessary because he may be using his spasticity to hold up his head or to stand during transfers. As the spasticity decreases, weakness may become severe and the patient will choose to stop the medication. Sometimes 10 mg a day is sufficient to give some benefit—one should be aware of individual variation in response and adverse effects. Asymmetry of response is seen sometimes. In general, less severe spasticity responds better than longstanding severe tightness. Occasionally the response is dramatic; at times only slight relief of muscle pain is achieved. When withdrawing the medications, do so slowly because rebound spasticity and hallucinations can occur.

Occasionally improvement in urinary tract function will be seen. A use for baclofen which is not mentioned in the product insert is as a treatment for trigeminal neuralgia. I have used it in patients allergic to dilantin or carbamazepine.

In summary, baclofen is a unique new drug that, if used carefully, offers significant relief of disabling spasticity, particularly in patients with MS.

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Migraine in Children

MIGRAINE IN CHILDREN may appear as the classical syndrome, beginning with painless preheadache phenomena manifested primarily as defects in visual function, followed thereafter by typical hemicranial pounding pain with associated nausea, vomiting and prostration. In addition, some migrainous episodes may occur in childhood in a considerably more recondite manner. Ehyai and Fenichel have described the cases of five patients with acute confusional migraine in which the primary complaint was confused agitation resembling a toxic metabolic psychosis. This syndrome occurred in either sex between the ages of 5 and 16 years. An acute confusional state was the initial manifestation of one of their migrainous patients, and in several children with this syndrome in previous reports. In the absence of a history of migraine there is considerable difficulty in making the diagnosis and therefore a family history of migraine becomes an important clue.

Headache may not be reported as a part of the acute confusional migraine syndrome, but typical migraine headaches always develop eventually. Confusion and disorientation are accompanied by agitation, a mixture of apprehension and combativeness. The duration of an attack is usually several hours but may be as brief as ten minutes or as long as twenty hours. The episode usually terminates in a deep sleep and the children appear to be normal on awakening. Of the five patients in the report by Ehyai and Fenichel, four had recurrent episodes of acute confusional migraine that tended to cluster over a relatively brief period of days or months. The mechanism is believed to be cerebral ischemia of one or both hemispheres.

In general, no specific therapy is required for acute confusional migraine beyond reassurance of the family and patient of the benign nature of the attack and its relationship to the migraine process. Ergot compounds are not necessarily helpful since many of the complaints are thought to be related to intracranial vasoconstriction. Should vascular headache appear subsequent to the development of acute confusional migraine, ergot compounds in standard doses can be employed.

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Epsilon-Aminocaproic Acid for Subarachnoid Hemorrhage

EPSILON-AMINOCAPROIC ACID (EACA, Amicar) has been shown to be effective in reducing the frequency of renewed bleeding in patients with subarachnoid hemorrhage. This drug is an inhibitor of fibrinolysis and probably acts by inhibiting the synthesis of plasmin from plasminogen and also the direct effect of plasmin. It probably acts by competitive inhibition of the activator that converts plasminogen into active plasmin. In a cooperative study, Nibbelink and co-workers documented the effectiveness of EACA in decreasing the frequency of renewed bleeding in patients with subarachnoid hemorrhage. Chowdhary and associates also showed in a controlled clinical trial that EACA was effective in reducing immediate recurrence of spontaneous subarachnoid hemorrhage. There have been some reports indicating that EACA may not be effective, but most of these studies have only included a few patients, and often they did not use controls.

EACA is used during the first two weeks of a subarachnoid hemorrhage while waiting for surgical therapy, if such is considered possible and indicated. It is during the first two weeks that recurrent hemorrhage or renewed bleeding is most likely, probably in part because of increased plasminogen levels in the cerebrospinal fluid at this time. EACA should be used carefully and fibrinolytic assays may possibly be helpful in monitoring the therapy.

EACA is usually given at 1 gram every hour orally or through a nasogastric tube or intravenously by constant infusion. When given intravenously it should be given slowly, otherwise it may induce significant hypotension, arrhythmias or bradycardias. The most common side effects are nausea, diarrhea and vomiting. Less likely to occur are dizziness, nasal stuffiness, headache or rash. There have been some cases of mild to moderate muscle tenderness or necrosis (or both) associated with its use. There have been a number of complications possibly associated with EACA therapy; however, because patients are ill and bedridden it is uncertain if the frequency or the actual cause of the side effects can definitely be attributed to the EACA therapy. Such possible complications may include intracranial vascular thrombosis, arteriolar-capillary fibrin thrombi or extracranial vascular thrombosis such as in the coronary, gastrointestinal or renal vessels. The occurrence of pulmonary emboli originating from deep vein thrombosis has also been considered to be a side effect of the drug. Possible confirmation of these complications has been made in some cases by biopsy or autopsy material.

If EACA is used carefully and appropriately, it will have a significant therapeutic benefit in reducing the initial morbidity and mortality in this life-threatening situation.

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Evoked Cerebral Potentials

EVOKED CEREBRAL POTENTIALS recorded by newer computer techniques have recently become a widely used means of documenting, discovering and further defining lesions in the central nervous system. Tests are now available for examining visual, auditory and somatosensory (posterior column) pathways. Frequently, lesions show up on evoked potential tests but not on any other tests. Indeed, sometimes *silent* lesions are found despite a normal physical examination and history for that pathway.

A major use of evoked potentials is to find demyelinating lesions. These show up as delays in the time between the stimulation and a measured brain electrical response. In cases of suspected multiple sclerosis (MS) about half of the patients with no known brain stem problems nevertheless have abnormal brain stem auditory evoked potentials. Likewise, about half of these patients

with suspected MS without known optic tract disease have abnormal visual evoked potentials, and about half of patients with suspected MS without known posterior column disease have delayed somatosensory evoked potentials. Consequently, a panel of such tests is very useful in determining if a patient who presents with his first single neurological deficit and really has lesions in multiple locations is more likely to have multiple sclerosis.

Even higher rates of delayed evoked potentials are seen in patients with definite MS or those who have had signs or symptoms of abnormalities in the respective sensory modalities. In some groups, abnormal results are found in 95 percent of patients.

More recently it has become evident that other pathologic conditions besides demyelination can cause abnormal evoked potentials. Certain types of compression (such as cerebellopontine angle or brain stem tumors) or degenerative disease (Parkinson disease, for example) cause similar abnormalities. Test results, therefore, should be interpreted as showing locations of disease rather than as pathognomonic of demyelination.

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Microsurgical Treatment for the Ischemic Cerebral Vascular Accident

TRANSIENT ISCHEMIC ATTACKS (TIA's) of the brain cause reversible neurological symptoms and signs, such as unilateral amaurosis, hemiparesis and dysphasia. Although these ischemic attacks may be due to cardiovascular disease, they are most commonly caused by stenosis of some portion of the internal carotid artery. In general, TIA's herald the coming of a major irreversible stroke, one of the leading causes of death and disability in the United States. Consequently, it is essential to diagnose TIA's accurately in the early phases in order to institute appropriate medical or surgical treatment (or both). Ultimately, this often requires contrast cerebral angiography of the cervical and intracranial carotid and vertebral basilar artery systems to determine areas of stenosis or occlusion. Fortunately, the potential risk of serious bodily injury by transfemoral angiography under local anesthesia is only about 0.5 percent.

If severe stenosis of the cervical carotid artery is discovered, especially with atherosclerotic plaques from which platelet emboli may be arising and causing TIA's, then a carotid endarterectomy-type operation is indicated. However, if there has been a total occlusion of the cervical internal carotid artery, or if there is stenosis of the cavernous sinus carotid artery or the middle cerebral artery, then a microsurgical revascularization operation of the brain should be considered.

The most common and acceptable operation is a microvascular anastomosis between the superficial temporal artery and the middle cerebral artery (STA-MCA) originated by two neurosurgeons, Donaghy and Yasargil, in the late 1960's and used clinically since 1970. In the past nine years a few thousand of these operations have been successfully carried out. Neurosurgeons experienced with this technique have achieved a patency rate above 90 percent. As the weeks and months pass after the operation, the STA-MCA anastomosis enlarges, producing increased blood flow to the ischemic cerebral hemisphere, usually eliminating the TIA's and substantially reducing the risk of stroke. Thus, lesions producing TIA's considered previously to be inoperable or inaccessible can be bypassed by a STA-MCA microvascular anastomosis procedure.

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Valproate: Newest Anticonvulsant

IN 1977 SODIUM VALPROATE (valproic acid, dipropylacetic acid [DPA], Depakene) burst upon the American medical scene amid much publicity. It became available in the United States the following year. A wholly new agent with a potentially different mode of action, it had been effective in Europe against a wide range of seizure types.

Among 2,031 patients treated here and abroad, many resistant to all other available drugs, the

results were impressive. Some 44 percent experienced a greater than 75 percent reduction in seizure frequency; 25 percent were slightly improved; 31 percent were considered treatment failures. DPA is most effective in generalized and least effective in focal epilepsies. It has been useful in both adults and children, when administered alone and with other anticonvulsants. It should be noted that valproate is FDA-approved only for use in absence seizures.

DPA probably will become the drug of choice in myoclonic and akinetic seizures, where only clonazepam has previously been helpful. Valproate is a welcome addition to the treatment of infantile spasms, for which adrenocorticotropic hormones and ketogenic diets are therapies of desperation. Its role in any but intractable tonic-clonic seizures is limited, for the present author, by its short half-life which requires multiple daily doses, and by possible toxicity. Refractory status epilepticus may respond to administration by gavage or by rectal suppository.

DPA has been advocated for the treatment of typical and atypical absence attacks (staring spells with or without automatisms). It is undoubtedly effective in these cases, but should probably be restricted to intractable cases, pending elucidation of toxicity. For prophylaxis of febrile convulsions, DPA has the advantage of less sedation than traditional therapies, but the same reservations apply.

Valproate is rapidly and completely absorbed after oral administration. Serum levels peak at one to four hours. In animals, DPA reaches the brain within minutes. The drug is highly (90 percent to 95 percent) protein-bound, but widely distributed. It crosses the placenta and enters (though at lower concentrations than primidone) human breast milk. After omega-hydroxylation and glucuronide conjugation by the liver, the drug is mostly excreted in the urine. Hepatic dysfunction is a relative contraindication to its use. Plasma half-life is 8 to 15 hours: less in children and in patients receiving phenytoin, phenobarbital, primidone, carbamazepine or ethosuximide. American investigators have used up to 50 mg per kg of body weight in adults. Standard adult schedules start with 250 mg twice a day, increasing at three to seven day intervals until control, toxicity or a maximum dose of 2,400 to 2,600 mg is achieved. Use of other anticonvulsants is monitored but maintained; maximum benefits from DPA may be deferred two or more weeks. The mechanism of action is unknown.

In summary, valproate is a major addition to the anticonvulsant armamentarium. Alone and with other drugs, it will find its place as experience with its use and toxicity grows.

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Meralgia Paresthetica

THE SYNDROME of numbness, tingling, burning or pain in the anterolateral thigh was first described in 1885 and later named meralgia paresthetica (*meros,* thigh; *algos,* pain). This mononeuropathy of the lateral femoral cutaneous nerve is a rare cause of severe pain; however, the paresthesias associated with this entity are more common than previously recognized and the syndrome is frequently misdiagnosed.

Typically, meralgia paresthetica is first seen in middle age and is a sporadic affliction. Nevertheless, the duration of symptoms before diagnosis may be quite variable, ranging from weeks to many years. There is a frequent association with obesity and the condition is reported to be bilateral in 8 percent to 12 percent of the cases.

It is thought that the long course and unique anatomical relationships of the lateral femoral cutaneous nerve make it particularly susceptible to mechanical forces. The nerve exits the lumbar plexus and passes beneath the psoas muscle, curving and descending to the level of the anterior superior iliac spine. It is here that the nerve angles sharply downward and passes under or through attachments of the inguinal ligament. Finally, the nerve pierces the overlying fascia and enters the anterolateral thigh.

The cause of meralgia paresthetica is occasionally identifiable. However, most cases are idiopathic. Reported antecedents of the syndrome include local trauma, pregnancy, intrapelvic disease, seat belts, braces, local tumors, disc lesions and prolonged hip extension. In a recent anatomical study, Edelson and Nathan found that in 51 percent of unselected adult autopsy cases there was a significant enlargement at the ligamentous stress point. The authors postulate that this pseudoganglion results from mechanical irritation and

may play a role in otherwise idiopathic cases of meralgia paresthetica.

Treatment depends largely upon a patient's history. In many persons relief is obtained from benign neglect or weight reduction, while in others there is response to local injections of lidocaine or steroids. In selected cases surgical manipulations, such as decompression, lateral transposition or complete transection of the nerve, have been employed successfully.

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Rehabilitation of Patients With Stroke

PATIENTS WITH A completed stroke and moderate to severe functional deficits can be rehabilitated and returned home, rather than sent to a chronic care facility.

A patient with an acute stroke who is not independent enough to return home when medically stable should ideally be transferred to the intensive, multidisciplinary, inpatient program of a regional rehabilitation center that treats at least 200 patients each year. Duration of inpatient rehabilitation ranges from 4 to 10 weeks, depending on the severity of neurologic and functional deficits and the degree of independence in activities of daily living necessary to live at home or in a board-and-care facility.

Factors that have negative effect on outcome of rehabilitation include long onset before admission to a specialty center, severe perceptual or cognitive dysfunction, and poor motivation. Severe weakness, sensory loss, dysphasia or visual field loss, and age or underlying medical problems may slow progress, but they are often overcome. These are not contraindications to a trial of formal rehabilitation.

With intensive inpatient therapy, about 80 percent to 85 percent of survivors of stroke will return home. About 80 percent will be independent in mobility and 60 percent will be independent in self care. Improved functional gains, especially for dressing, bowel and bladder function, transfers and walking may develop with therapy even one year after onset of stroke, and are maintained by most patients. Aphasic patients make significant gains with formal speech therapy compared with untreated aphasic patients; comprehension tends to improve more than expressive tasks. No single therapeutic modality seems more effective than another. Therefore, an eclectic approach to deal with a patient's particular neurologic and functional disability seems warranted.

Unfortunately, the natural history of recovery of a stroke patient with a particular set of symptoms, signs, laboratory studies, and findings by angiography and computerized tomography has not been available. Thus the value of specific neuromedical and rehabilitative interventions will be uncertain, until similar patients are compared prospectively. The national Stroke Data Bank Pilot Project has recently begun to address this problem.

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Management of Cluster Headaches

THE MAIN FEATURES of cluster headaches include extremely severe unilateral pain which is most often periorbital, of short duration (20 to 90 minutes), and associated with ipsilateral ptosis, miosis, conjunctival injection and rhinorrhea. In many patients there is a periodic "clustering" of headaches followed by an extended remission period. This is termed episodic cluster. A chronic type of cluster headache has recently been identified. In this category typical cluster headaches occur without any remission period. A rare subgroup of the chronic variety has recently been described as chronic paroxysmal hemicrania (CPH), based on its unique therapeutic response. This type of clinical classification is useful in choosing the appropriate drug in a disorder that is difficult to treat.

In a patient with episodic cluster headaches, especially with a clock-like regularity to the attacks, 1 to 2 mg of ergotamine tartrate administered orally an hour before the anticipated time of the headache provides the best prophylactic therapy. Most often a bedtime dose is sufficient to prevent headaches at night. The timing of the headache may occasionally change after initiating this form of treatment, and one may have to "chase the headache" with ergots. If the timing is erratic

or more than two attacks a day occur, 6 to 8 mg per day of methysergide is recommended. Close clinical follow-up with an awareness of the potential for retroperitoneal fibrosis is necessary. Continuous use of this medication for more than six months without a drug-free interval of three to four weeks is not recommended. If these measures fail, a short course of steroids (40 mg of prednisone) for five to seven days with rapid tapering of the dosage over three weeks induces a remission in 75 percent of patients.

In chronic cluster headaches the best form of therapy is 300 mg of lithium carbonate given two to four times a day, with care taken to maintain a blood level below 1.2 mEq per liter. More than 85 percent of patients respond favorably to this regimen. In the subgroup with CPH, indomethacin (25 to 50 mg three times a day) is very effective.

Acute attacks of either type of cluster headaches are best treated symptomatically with sublingual ergotamine preparations (2 mg) or inhalation of 100 percent oxygen at 5 to 7 liters per minute for ten minutes.

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Lacunar Infarction

LACUNES ARE DEFINED pathologically as small trabeculated cavities (0.5 to 20 mm) found in the deeper parts of the brain such as the putamen, pons, thalamus, caudate and internal capsule. These lesions are a result of ischemic infarction in the distribution of penetrating arteries varying in diameter from 80 to 1,000 μ. Although this lesion and some of its clinical correlates were described before the turn of the century, the syndrome of lacunar infarction was largely ignored by modern clinicians until the exquisitely detailed studies of C. Miller Fisher firmly established the clinical and pathological characteristics of this process. The magnitude of the problem is indicated by the prospective data of the Harvard Cooperative Stroke Registry; 20 percent of all patients entered were diagnosed as having lacunar infarction.

Fisher studied the brains from 1,042 consecutive autopsies and found lacunes in 11 percent. Most of the lacunes were small (1 to 4 mm) and located in the putamen (37 percent). Ten percent were found in the internal capsule. The lesion was almost exclusively confined to patients with a history of hypertension and strongly correlated with the presence of moderate to severe atherosclerosis. Two types of arterial pathologic conditions are found to underlie lacunes: lipohyalinosis and focal atherosclerisis. Both are essentially unique to cerebral vasculature. Lipohyalinosis affects cerebral arteries 80 to 300 μ in diameter and produces mainly small lacunes averaging 2 mm in diameter which are often found as asymptomatic lesions in hypertensive patients at autopsy. Focal atherosclerosis affects larger penetrating arteries 400 to 1,000 μ in diameter and produces larger lacunes (rarely up to 2 cm in diameter) which are probably responsible for most symptomatic lacunar infarcts. Pathologically, focal atherosclerosis consists of isolated miniature plaques of large fat filled macrophages.

Fisher has described four clinical syndromes resulting from lacunar infarction at different anatomic sites. The most common lacunar stroke (accounting for approximately 50 percent of all such strokes) is pure motor hemiplegia. This is a pure motor syndrome of hemiparesis involving face, arm and leg with associated long tract signs and often dysarthria. The responsible lesion is located in the contralateral internal capsule, pons or medulla (face is spared with the latter). A second syndrome is pure sensory stroke characterized by the onset of paresthesias and mild sensory loss over one entire side of the body with little or no functional disability. The lesion is located in the contralateral posteroventral nucleus of the thalamus or sensory portion of the internal capsule. The third syndrome is ataxic hemiparesis characterized by the development of difficulty in walking and ipsilateral arm incoordination. A mild hemiparesis is present with ipsilateral ataxia of the limbs. The lesion is located in the contralateral basis pontis. The fourth clinical pattern is referred to as the *dysarthria clumsy hand syndrome* and is characterized by moderate dysarthria, facial weakness and clumsiness of one hand. The lesion is in the contralateral pons or internal capsule. Other lacunar syndromes will undoubtedly be described following further clinical-pathological correlation.

Transient ischemic attacks may precede lacunar infarction in a fourth of patients and usually occur within 24 hours of the stroke. Stroke onset is more often gradual or saltatory than sudden. Most patients in whom a lacunar stroke develops can look

forward to moderate to excellent recovery even if their initial symptoms were quite disabling. Because of the unique pathologic features of lacunar infarcts, headache, obtundation, cortical deficits and seizures are notably absent and no electrocardiographic abnormalities are seen. A computed tomographic scan may either be normal or show a small enhancing lesion in the distribution of a penetrating artery, and it is an important diagnostic study since the clinical features alone can be misleading. Using computed tomography, Weisberg studied cases of pure motor hemiplegia and found a variety of causes. Thus, the diagnosis of lacunar stroke is made when the neurologic features fit one of the described lacunar syndromes, headaches and the like are absent, and diagnostic studies are compatible.

Treatment consists of controlling existing hypertension in about 80 percent of these patients; however, blood pressure should be lowered cautiously in acute stroke victims because abrupt decreases may precipitate further neurologic symptoms. Because of the location and size of involved vessels, angiography and vascular surgical procedures are not indicated. Anticoagulation may be beneficial if transient attacks of pure motor hemiplegia are occurring, but prolonged anticoagulation is usually not recommended. The role of antiplatelet agents in such patients has not been assessed.

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EDITORIALS

The Four Dimensions of Medicine

It is at least interesting, and there may be some profit from doing so, to consider medicine and health care in four dimensions. These dimensions appear to have evolved and to continue to be evolving over time. The oldest, and yet some would say the newest, considers caring for the patient as a whole person and its caveat was and is "do no harm" on the one hand, and seek to promote good health on the other. This very ancient and very modern dimension is currently under examination in a forum being conducted in this journal.

Curative medicine, a second dimension, is in apparent ascendency at this time. It began its rise at some point around the turn of the century when it was said that for the first time a patient stood a better than even chance of benefiting from an encounter with a physician. As medical science has developed, curative medicine has made dramatic and even spectacular progress, but this somewhat at the expense of wholism and the caveat to do no harm.

As curative medicine has gained ground, physicians and the public are beginning to be more interested in and concerned with prevention, or the stage or dimension of medical practice and health care that precedes the need for curative medicine. The idea of prevention in medicine and health care is rapidly gaining ground both in terms of what it can actually accomplish and, unfortunately, in a probably misplaced public expectation that it will actually reduce the dollar cost of health care. The prevention dimension of medicine will surely expand and gain strength in the 1980's, as indeed it should, as our knowledge of what to do and how and when to do it inevitably grows.

A fourth dimension of medicine and health care is beginning to concern itself with what happens subsequent to the curative phase. There is more interest in rehabilitation and quality of life for the treated (or untreated) person, as well as increasing concern with the broader social implications of the growing success of curative and preventive medical services, with much of which the medical profession has found itself ill prepared to deal. Among these are bioethical social problems, cost problems and political problems of how to manage such a complex, interdependent enterprise which touches so closely upon the freedom and well-being of individual citizens and yet has enormously important ramifications for society as a whole which cannot be ignored.

These four dimensions—(1) wholism and do no harm, (2) curative medicine, (3) prevention and (4) the consequential phase, if you will (that is, the short-range and long-range consequences of prevention and curative medicine)—are a kind of interactive continuum in one sense. But more than that, they are the dimensions of medicine and health care as we enter the decade of the 1980's. There is enormous potential for growth and development in each of them and this will surely occur. Each is properly the concern of every individual practitioner, as well as of the medical profession as a whole. There is a role and need for scholarship and for leadership. However, it remains to be seen how well—both individually and collectively as a profession—we will recognize these old and new challenges, and how well we will rise to meet them as we plunge into this new decade, which promises to be the most complex and fascinating one yet for medicine.

—MSMW

Cryptococcosis

WHEN A PATIENT IS DYING of a disease, the rarity of the disease offers scant consolation to the patient or physician. And somehow the rarity seems relatively insignificant to both. The inherent tragedy is compounded when death occurs from a curable, albeit rare, disease. Perhaps one should compute a *significance factor* for rare diseases, which would be the product of the incidence times the percent mortality untreated times the percent cured by appropriate treatment. Thus, the significance factor for cryptococcal meningitis would be very roughly 0.2 cases per 100,000 people per year times 100 (percent fatality untreated) times 55 (percent cured with appropriate therapy). From this vantage point, the special conference on cryptococcosis in this issue is seen not as an academic exercise in minutiae but as a useful guide for busy practitioners.

For those physicians using guides like this to assist them down the entire road of diagnosis, treatment and follow-up, a useful supplement would be a "Guide to Common Pitfalls." For cryptococcal meningitis, the list of things physicians most often do not know might include the following: (1) several milliliters of cerebrospinal fluid (CSF) may need to be cultured to grow *Cryptococcus neoformans;* (2) weekly CSF fungal cultures are invaluable in deciding when to end therapy; (3) when amphotericin B therapy is changed from every day to every other day, the dose must be doubled; (4) flucytosine dosage must be reduced in azotemic patients to prevent severe leukopenia, thrombocytopenia and enterocolitis, and (5) routine posttherapy lumbar punctures and computerized axial tomographic (CAT) scans may detect relapse or hydrocephalus, respectively, before permanent sequelae occur.

Since the time the conference reported in this issue was held, the collaborative cryptococcal meningitis therapeutic trial has been published.[1] Efficacy of the two-drug regimen in this study can be seen easily, but the 30 percent incidence of flucytosine toxicity should not be overlooked. Although these toxic reactions were not life-threatening in study patients, fatalities have been reported in the literature. There is still no easy regimen for treating patients with cryptococcal meningitis. Miconazole has proved relatively nontoxic, but there is no convincing evidence that the drug is effective at all in cryptococcosis. For the present, physicians caring for patients with cryptococcosis must remain tormented by the fact that this disease is curable yet the day-to-day management is often extraordinarily difficult. This predicament, of course, is not new:

> Diseases desperate grown
> By desperate appliances are relieved,
> Or not at all. (*Hamlet* IV:iii,9)

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Unanswered Questions About Tubulo-interstitial Nephropathies

TWENTY YEARS AGO the Medical Staff Conference by Dr. Cogan, which appears elsewhere in this issue, would have been entitled "Chronic Pyelonephritis" and a bacterial cause for the resulting chronic interstitial scarring would have been the only theme discussed. Fortunately, new knowledge has broadened both the known and suspected causes of tubulo-interstitial disease, and these are appropriately emphasized by Dr. Cogan's discussion.

That tubulo-interstitial disease is a significant entity can be appreciated from reviews of the various causes ascribed to end-stage renal disease. At present it is estimated that in a quarter to a third of patients with end-stage renal disease who are evaluated for renal replacement therapy a diagnosis of chronic interstitial nephritis eventually can be made. Of equal importance is the number of drugs that have been identified as causing acute interstitial nephritis through the immunologic mechanism described by Dr. Cogan. This list grows each year and, in addition to the penicillin and penicillin-like compounds, includes the thiazide diuretics, furosemide, phenindione, sulfonamides, diphenylhydantoin, allopurinol, azothioprine and rifampin.

However, when one examines the various

causes for chronic interstitial nephritis, the evidence supporting an immunologic basis is less compelling. A feature common to many of the proposed causes of chronic tubulo-interstitial disease is the associated renal medullary damage. This is best recognized in conditions such as analgesic nephropathy, urinary tract obstruction with reflux, diabetic nephropathy, sickle cell disease, Balkan nephropathy and various other diseases of the kidney. The contribution of bacterial infection to the incidence of chronic interstitial disease is in dispute. "Present evidence indicates that bacterial infections of the urinary tract can produce serious renal disease only when associated with other conditions that are by themselves damaging to the kidney and act to increase the susceptibility of the kidney to infection"; so state Freedman and Andriole.[1] For completeness, several of the congenital metabolic defects have associated renal lesions which are tubulo-interstitial in character—Wilson disease, the Alport syndrome, primary hyperoxaluria and cystinosis. Finally, gouty nephropathy, nephrocalcinosis, hyperphosphatemia, heavy metal poisonings (chronic), disseminated intravascular coagulopathy and radiation nephritis all result in tubulo-interstitial disease of varying severity.

By and large, as pointed out by Dr. Cogan, treatment has remained symptomatic, although a recent report from Galpin and co-workers[2] suggests that short-term high dose steroid therapy may speed the recovery of renal function following drug induced acute tubulo-interstitial nephropathy. The problem of analgesic nephropathy continues to be distressing because it is a totally preventable entity provided it is recognized early and the patient will abstain from further analgesic abuse. Often the psychological dependence defeats attempts to withdraw the analgesic and there are multiple examples in every nephrologist's practice of patients who have received renal transplantation or who are undergoing dialysis for a disease for which we not only understand the cause but also the means of prevention.

Much information concerning tubulo-interstitial disease has been collected in the last 20 years, but unanswered questions still remain. Are many of the cases of chronic tubulo-interstitial disease examples of recurrent acute episodes that are subclinical? What is the role of environmental exposure in causing interstitial disease of the kidney? What explains the pronounced geographic discrepancies in the worldwide distribution of analgesic nephropathy? It is hoped that when a Medical Staff Conference in THE WESTERN JOURNAL OF MEDICINE next addresses tubulo-interstitial nephritis, some of these questions can be answered.

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Discrimination in High Places

YET ANOTHER INCREASE in the Social Security tax in January of this year again focuses attention on the behemoth which seems to take so much from us and to give so little in return. Its promise as a retirement system providing lifelong security is proving to be a tragic disappointment if not a hoax to those who depend upon its retirement benefits to survive in an economy of runaway inflation. Medicare has become a generally welcome benefit equally for rich and poor. The role of Social Security welfare has been the subject of much criticism. Its principle is that those who are working are taxed to provide benefits to retirees and to other beneficiaries who are in need of one or another kind of welfare aid. The result is something of a hodgepodge of earned and unearned benefits financed by some but not all who work.

It surely seems that if the social security provided by this system with its ever increasing tax were good for some Americans it would be good for all and that all who work should be required to participate. But this is not the case. Those who should know best, the federal employees, who number among the millions, have succeeded in remaining outside the system for all these years and pay no Social Security tax. It would seem that this is something like discrimination in high places, if what is good enough for the public is not good enough for those whom the public pays to work in the federal government. It sticks in this craw.

—MSMW

JCAH's New Quality Assurance Standard

THE NEW quality assurance standard discussed by John Affeldt elsewhere in this issue and first announced by the Board of Commissioners of the Joint Commission on Accreditation of Hospitals (JCAH) in April 1979 is welcomed. It embodies a shift in approach to the process of accreditation of hospitals. For example, numerical requirements for medical audit are no longer prominent in the accreditation grading.

The following are major themes of the new standard: coordination of existing quality assurance activities in hospitals, broader approaches to quality assurance by including or developing alternate methods of assessing quality of care, and emphasis on institutional responsibility, directed by the Board, for quality of care in hospitals.

The proposed program to comply with the standard is, at the moment, a concept. Few details of implementation are available. It seems the coordination-integration of existing activities will require each hospital to develop a written plan through which committee activities will be interrelated in the process of identifying problem areas and assessing quality of care. Such integration will presumably require a person to be responsible for the coordinating activities. A similarity which immediately comes to mind is the current position of coordinator for the utilization review committee. However, the scope of activities suggested in the new standard includes access to confidential and sensitive data such as that generated in a credentials committee, or in a departmental morbidity-mortality committee, or from incident reports in a risk management program, or even financial data concerning the hospital. This coordinating person or committee, presumably from within the medical staff, will need access to the board of directors of the hospital, and will provide pertinent information concerning problem areas within the system. Problem elimination as a corporate responsibility is reemphasized.

The thrust of the new standard is toward concurrent review of activities of all hospital personnel, not just physicians and nurses, in the common interest of improved quality of care. More emphasis will be placed upon outcomes than on process in the identification of problem areas. Review will reach into management areas as well as to the direct patient care items.

The date of formal implementation of the standard has not yet been announced, and implementation probably will not take place for at least a year. Certain details are not clear at this time. Exactly how compliance with the conceptualized standard will be measured in the process of accreditation of hospitals remains to be clarified. Although the plan relies on evaluation of outcomes, one cannot avoid wondering whether the survey procedure itself simply will look at the process of quality assurance steps, and thus become another paper chase. Another unknown, at the moment, is the relationship of this standard with potential requirements of Professional Standards Review Organizations.

Finally, notable for its absence is any reference to the relationship of this new JCAH focus to the existing peer review of quality care, such as is done by California Medical Association physicians in the CALS (Consolidated Accreditation and Licensure Surveys) program. The long-standing belief that peers should review quality of care rendered in hospitals underlies this arrangement. Yet, not one word about this is contained in the paper by Dr. Affeldt. Such an omission seems to question the important role of peer review in any quality assessment program.

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CASE REPORTS

Refer to: Ylvisaker JT, McDonald GB: Sexually acquired amebic colitis and liver abscess. West J Med 132:153-157, Feb 1980

Sexually Acquired Amebic Colitis and Liver Abscess

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AMEBIASIS has long been recognized as a possible consequence of travel to areas where the parasite is endemic.[1] Various forms of the disease also have been seen in people with no travel history outside the United States—particularly in rural areas, in the southern states, in lower socioeconomic groups and in institutions for the mentally retarded.[2] More recently, amebic dysentery was described in the male homosexual communities of New York and San Francisco.[3-5]

We report the cases of two homosexual men with amebic dysentery and liver abscess. These cases emphasize the difficulties of diagnosing intestinal disorders in homosexual men, and show that amebiasis in these patients may be a virulent illness.

Reports of Cases

CASE 1. A 37-year-old man entered Harborview Medical Center in Seattle, in August 1975, with a two-week history of bloody diarrhea, a week of fever, four days of right shoulder pain, and two days of right chest pain and dyspnea. He had a past history of treated syphilis; rectal culture for gonorrhea was negative two weeks before admission. He was an admitted homosexual who was visiting Seattle from New York City, with no history of travel outside of the United States. Physical examination showed a temperature of 38.8°C (101.8°F) with no chest or abdominal abnormalities. At sigmoidoscopy, the rectal mucosa was diffusely friable, with whitish exudate from the dentate line to 25 cm. Laboratory studies gave the following values: hematocrit was 48 percent; leukocyte count, 11,600 per cu mm with normal differential; bilirubin, 1.2 mg per dl; alkaline phosphatase, 138 IU per liter (normal, less than 90); serum glutamic oxaloacetic transaminase (SGOT), 24 units per ml (normal, less than 28); serum glutamic pyruvic transaminase (SGPT), 53 units per ml (normal, less than 30), and prothrombin time, 14.5 seconds (control, 13 seconds). An x-ray study of the chest showed atelectasis at the left lung base. Treatment with sulfasalazine (Azulfidine) for presumed ulcerative colitis was started.

Two days following the patient's admission, right upper quadrant abdominal pain and a pleural friction rub were noted. A technetium liver scan showed a single defect 4 to 5 cm in size in the dome of the right lobe. Sigmoidoscopy then showed a diffusely abnormal mucosa with small punctate ulcers; wet-mount examination showed trophozoites of *Entamoeba histolytica*. (Rectal biopsies also showed the organism.) Stool culture was negative for bacterial pathogens as was a rectal culture for *Neisseria gonorrhoeae*. Treatment with metronidazole (Flagyl), 750 mg three times per day, was started and there was substantial improvement by the following day. Three days later, the patient was discharged afebrile and without diarrhea or abdominal pain. He immediately left the Seattle area and has been lost to follow-up. After discharge, his acute indirect hemagglutination titer for amebae returned as positive at 1:128.

CASE 2. A 27-year-old man was admitted to the Seattle Veterans Administration Hospital in January 1977 with a four-day history of bloody diarrhea, fever, chills and crampy right upper quadrant abdominal pain, and a one-day history of right shoulder pain. In 1974 he had been evaluated for mild rectal bleeding; a barium enema study showed no abnormalities and sigmoidoscopy showed only hemorrhoids. Four months before admission to hospital, the patient reported bloody diarrhea and tenesmus, which had been diagnosed

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elsewhere as ulcerative colitis on the basis of a rectal biopsy. Treatment was begun with sulfasalazine and steroid enemas with resolution of symptoms over two to three weeks. Six weeks before admission the patient had recurrent mild rectal bleeding which resolved spontaneously.

His past history included recurrent asymptomatic rectal gonorrhea, his last positive culture being six months before his admission to hospital. In October 1974 hepatitis B developed in the patient, with persistent positive serum HBsAg. His last recorded SGOT was 180 units per ml in May 1975. He had lived in Seattle for the past four years and had not traveled outside the United States since being in Vietnam from 1970 to 1971—there had been no history of diarrhea or dysentery while there. He described homosexual activities with many different partners, one such contact occurring five months before admission. This partner had recently returned from Southeast Asia complaining of rectal pain and an examination had shown "proctitis without blood or ulcerations."

Physical examination of the patient showed an ill-appearing, thin man with a temperature, taken orally, of 37.9°C (100.2°F). Abdominal examination showed right upper quadrant tenderness without hepatomegaly. Sigmoidoscopy showed many well-circumscribed ulcers, with slightly friable and edematous intervening mucosa. Trophozoites of *Entamoeba histolytica* were found on examination of stool, and rectal biopsies showed many organisms as well (see Figure 1).

Cultures for *Neisseria gonorrhoeae* and other bacterial pathogens were negative. Serum HBsAg was positive; VDRL was negative. Other laboratory studies gave the following values: a hematocrit of 36 percent, leukocyte count of 14,200 per cu mm with a normal differential and an erythrocyte sedimentation rate (ESR) of 52 mm per hour. Liver function studies showed normal bilirubin and alkaline phosphatase values with SGOT minimally elevated at 52 units per ml. A chest x-ray study showed no abnormalities and a technetium liver scan showed a single 5-cm defect in the dome of the right lobe (Figure 2A).

The patient was treated with metronidazole 750 mg three times per day and tetracycline 500 mg four times a day with prompt clinical improvement. He was discharged afebrile three days after treatment was begun. Six weeks later, he was asymptomatic, findings of stool examination for amebae were negative and sigmoidoscopy gave normal findings. By June 1977, five months after discharge from hospital, the liver scan showed no abnormalities (Figure 2B). The indirect hemagglutination titer for amebae drawn during the acute illness was positive at 1:4,096.

Discussion

There have been several reports of intestinal amebiasis in the homosexual community,[6-9] including one of amebiasis in four homosexual men following one partner's travel to an endemic area.[10] The frequency of amebic dysentery in homosexual men in New York and San Francisco

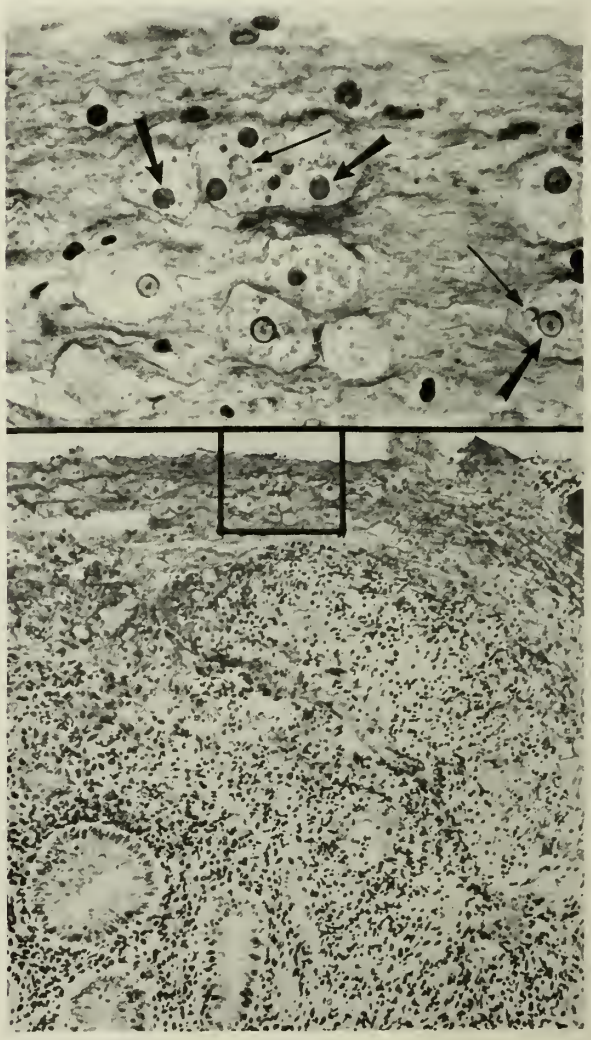

Figure 1.—Case 2. Rectal histology. **Above,** a high-power view of the boxed area, showing several trophozoites of *Entamoeba histolytica*. Large arrows point to typical spherical nuclei with central karyosomes and small arrows point to ingested red blood cells within cytoplasm. (Hematoxylin and eosin stain; reduced from ×200.) **Below,** a low-power view showing crypt destruction, inflammation and an overlying exudate. (Hematoxylin and eosin stain; reduced from ×40.)

has been noted[3-5] and, in fact, our first patient was visiting Seattle from New York. In contrast to the illness described in these series, amebiasis in our patients was severe, with tissue invasion of colon and liver. We have no ready explanation for the severity of their disease—an invasive stain of *Entamoeba histolytica* may have been acquired,[11] or perhaps rapid passage of an avirulent strain through several hosts may enhanced its invasiveness.[12-14] Promiscuous sexual behavior might create the opportunity for such rapid passage.

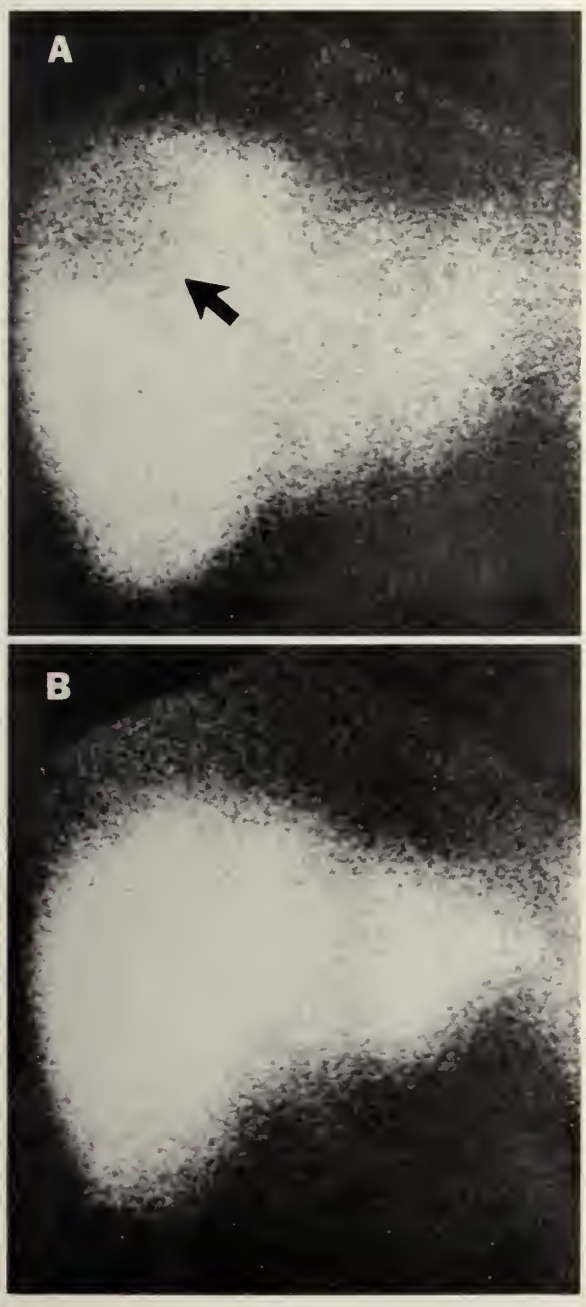

Figure 2.—Case 2. Technetium liver scans. **A**, during the patient's acute illness, showing a solitary 5-cm defect in the right lobe **(arrow)**. **B**, five months later, showing a normal liver.

Venereal transmission of amebiasis can occur by several routes. Amebic balanitis (caused by *E histolytica*) can occur after sexual contact with an infected woman;[15] vaginal infections are presumed to arise in the colons of women who practice poor hygiene.[16,17] However, recent reports describe penile amebiasis as a disease of homosexual men.[18,19] In neither of our patients were penile lesions present, but both gave histories compatible with fecal-oral transmission of the organism, either by rectal intercourse followed by oral-genital or oral-rectal contact among several partners.

Making the diagnosis of amebiasis in homosexual men with diarrhea may be difficult because typhoid fever,[20] shigellosis[21,22] and giardiasis[23-25] have been recently described in this population. Gonorrhea and syphilis must be also considered, although the former is frequently asymptomatic.[26-29] Bloody diarrhea (dysentery) in a homosexual man should strongly suggest shigellosis or amebiasis; the finding of fecal leukocytes would be consistent with either of these invasive diseases as well as ulcerative colitis, Crohn disease and *Yersinia* enterocolitis. However, the diagnosis of amebic colitis is critically important for several reasons: it is not self-limited, like the bacterial dysenteries; it is easily cured, unlike Crohn disease and ulcerative colitis, and it should not be empirically treated with steroids because of the danger of dissemination of amebae.

Misdiagnosis of amebic colitis is common where the disease is not endemic—this includes most of the United States.[30] Multiple fresh-stool examinations and direct scrapings of ulcerated rectal mucosa will generally show cyst and trophozoite forms of the organism. However, excretion of *E histolytica* may be intermittent or rare, particularly after administration of antibiotics (including sulfonamides) and cathartics; specimens obtained two to three days apart should be examined. Barium, magnesium, kaolin, bismuth and oily compounds can obscure the parasites and may alter the appearance of trophozoites.[31] When the sigmoidoscopic appearance shows punched-out ulcerations with relatively normal mucosa in between, the diagnosis of amebiasis is strongly suggested.[1] However, other conditions, such as Crohn disease[32] and yersinosis,[33] may show similar

aphthous ulcerations of the colon. Unless wet mounts can be prepared and interpreted promptly, scrapings should be preserved for analysis in polyvinyl alcohol.

Confusion may arise when the rectal mucosa is diffusely abnormal, simulating idiopathic ulcerative colitis.[31,34] Rectal biopsies are not as sensitive as thorough stool and scraping examinations, and when the biopsy does not show the organism, the rest of the histologic findings are entirely nonspecific.[34,35] However, serologic findings (indirect hemagglutination) are positive in 82 percent to 98 percent of patients with acute amebic colitis,[30,31] and should be routinely ordered when the cause of colitis is uncertain.

The combination of colitis and liver abscess should point to a diagnosis of amebiasis, although colitis need not be present in patients with liver abscess.[36] In fact, only 14 percent of a large series of more than 2,000 patients had diarrhea or dysentery at the time the diagnosis was made.[37] In a study of cases of amebic liver abscess in the United States, less than a third of the patients had diarrhea and in only 6 of 41 patients were there organisms in stool specimens.[38] Positive serologic findings for amebiasis are the rule with amebic liver abscess.[36] Whether a more invasive strain of the organism was responsible for the colitis/abscess presentation in our patients in unclear, but this possibility has been suggested.[11-14]

In both of our patients there were good clinical responses to oral administration of metronidazole, as has been reported for both colitis and liver abscess.[37-40] However, treatment failures have also been documented, and in some patients treated with metronidazole alone for amebic colitis, liver abscesses have developed.[39]

Although metronidazole, in a dosage of 750 mg three times per day for five to ten days, is probably the drug of choice for both amebic dysentery and extraintestinal amebiasis, there is concern about its potential carcinogenicity. Alternative drugs are available and their indications, dosages and toxicity have been recently reviewed.[1,13,41] Aspiration of amebic abscesses may be required, particularly if rupture into the peritoneum is imminent; our patients recovered uneventfully after receiving metronidazole alone.

There are several lessons to be learned from these two cases: (1) Sexually acquired amebic infections may be severe, presenting as dysentery, liver abscess or both. (2) The diagnosis of amebic colitis must be strongly considered in homosexual men with diarrhea, and can be made by thorough examination of stool specimens and rectal scrapings, with accompanying serologic studies. (3) The occurrence of liver disease in a homosexual man with or without diarrhea should prompt consideration of amebic liver abscess.

Summary

We have presented the cases of two homosexual men, each of whom presented with amebic colitis and liver abscess. Both responded to treatment with metronidazole. These cases illustrate the difficulties of diagnosing intestinal disorders in homosexual men and provide evidence that sexually transmitted amebiasis can be a virulent illness.

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Toothpick Perforation of the Duodenum

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TOOTHPICKS have acquired many uses in addition to their intended function of oral hygiene. They are widely used as eating utensils, for decoration and in the preparation of many foods. When employed to clean the teeth, toothpicks are rarely swallowed; those accidentally ingested have usually been involved in food preparation without the knowledge of the consumer.[1] The most important factor associated with ingestion of foreign bodies is the wearing of dentures;[2-4] persons with upper dental plates lack the tactile sensitivity of the palate that normally prevents such objects from being swallowed.

A swallowed toothpick becomes a surgical problem when it fails to pass spontaneously and perforates the intestine. This complication is not rare; toothpicks account for 10 percent of intestinal perforations by ingested foreign bodies.[5]

Report of a Case

A 54-year-old man was admitted to another hospital with an eight-day history of cramp-like abdominal pains and fever. A diagnosis of acute cholecystitis was made, and he was treated with intravenously given ampicillin and gentamicin without improvement. Exploratory laparotomy was done on the third hospital day and showed a normal gallbladder, although duodenitis was noted.

The patient continued to have spiking fevers to 40.5°C (105°F) postoperatively. X-ray studies of the upper gastrointestinal area done a week after the exploratory operation showed extravasation of retroduodenal contrast material from the second portion (Figures 1, 2). The patient was transferred to University of California, Los Angeles (UCLA), Hospital, where a diagnosis of perforated duodenal ulcer was made. Subsequent exploration showed considerable duodenal inflammation, especially along the lateral duodenal wall, with many retroperitoneal adhesions. No distinct abscess cavity could be isolated and intraoperative cholangiograms showed no abnormalities. The third portion of the duodenum was grossly strictured; this was opened, revealing an anterior ulcer, 1 cm in size, in the distal second portion. A probe was passed through the ulcer into the duodenal wall, tunneled into the pancreas, and finally passed into a cavity in the hepatoduodenal ligament (Figure 3). The ulcer base was oversewn. Further exploration in this area was deemed unsafe. The opened, inflamed duodenum was bypassed with a Billroth II gastrectomy. When the jejunum was opened during the gastrojejunal anastomosis, a wooden toothpick was discovered. The patient was discharged home on the 12th postoperative day.

Discussion

Ingestion of foreign bodies is a fairly common event which rarely causes problems; indeed, 80 percent to 90 percent of swallowed objects pass through the gut without complications.[2,6] How-

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Reprint requests to: L. William Traverso, MD, c/o Mrs. Seba Kolb, Editor, Department of Surgery 72-125 CHS, UCLA School of Medicine, Los Angeles, CA 90024.

Figure 1.—Anteroposterior view of a duodenal perforation with collection of contrast above the pyloric channel. Note duodenal narrowing distal to the perforation.

Figure 2.—Lateral view of the retroduodenal perforation and collection in the area of the hepatoduodenal ligament.

ever, objects not passed spontaneously can cause obstruction, perforation or bleeding.[1] Although less than 1 percent of retained foreign bodies injure the intestine,[7] perforation of the intestine is associated with high morbidity and occasional mortality; Maleki and Evans reported one death in 12 cases of foreign body perforation.[8]

Most persons who ingest nonmetallic foreign objects are unaware of swallowing them.[2,8-10] Toothpicks typically are ingested when they have been used either to fasten together parts of a food item or as a decoration.[1] Cooking softens the toothpicks, compounding the problem. A person who is an alcoholic or who eats rapidly has a greater chance of such accidental ingestion. Several authors have also emphasized the fact that 75 percent to 80 percent of cases of foreign-body ingestion with subsequent perforation were associated with denture use, due to a resulting lack of palate sensitivity.[4,8] Our patient, who wore full dentures, was totally unaware that he had swallowed a toothpick probably two weeks before admission to UCLA Hospital.

Without a history of ingestion, diagnosis of intestinal perforation by a foreign body is often difficult to make. There are usually a wide spectrum of clinical manifestations closely resembling other more common surgical disorders.[11] Acute appendicitis is a typical preoperative diagnosis when the ileocecal region has been perforated.

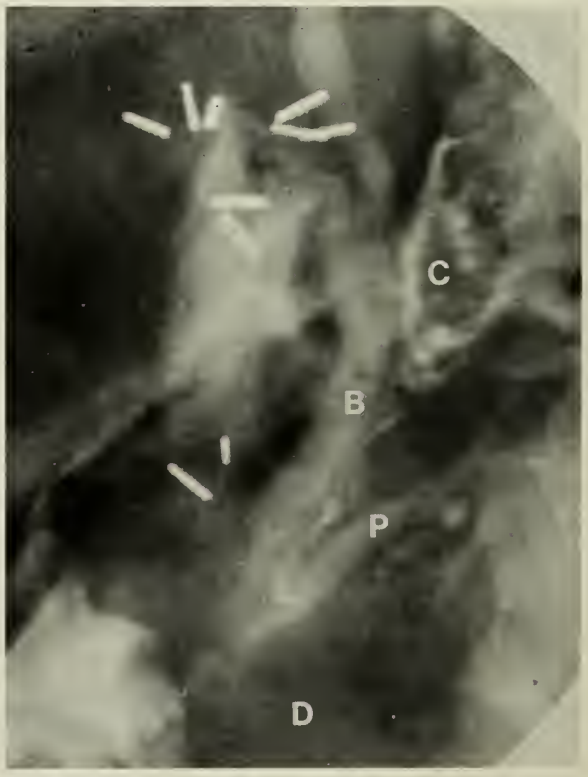

Figure 3.—Intraoperative cholangiogram showing the close relationship of the common bile duct **(B)**, pancreatic duct **(P)**, sinus tract with cavity **(C)** and duodenum **(D)**.

Small bowel perforation may closely resemble acute cholecystitis, and colon perforation may be confused with diverticulitis. Because an ingested toothpick usually does not perforate immediately, the acute development of pain, nausea, vomiting and general peritonitis is rare;[2] patients usually present with vague abdominal complaints. No specific clinical or laboratory tests exist to establish a correct preoperative diagnosis. X-ray studies are relatively useless because radiolucent toothpicks cannot be identified, and free air in the abdomen subsequent to perforation is rare.[1,3,11]

Foreign-body perforations have been found at points along the gastrointestinal tract from the stomach to the rectum, typically at areas of narrowing or acute flexure of the gut. From experimental work with dogs and cats, Carp[6] identified the points where sharp bodies usually arrest: (1) the junction of the second and third portions of the duodenum, (2) the ileocecal region, (3) the lumen of the appendix, (4) the junction of the cecum and ascending colon and (5) flexures and haustra of the large intestine. Although perforations in each of these sites have been reported, the ileocecal region is the most common location,[3] accounting for 73 percent of the cases presented by Macmanus.[5]

These intestinal perforations require surgical intervention; the specific procedure depends on the site of perforation and the presence of associated complications, such as abscess or sinus tract formation. Simple colon perforations are treated with primary closure alone or are combined with a diverting colostomy if complications are present. Cases involving the small bowel require resection of the injured area. While no specific treatment for duodenal perforations has been outlined in the literature, removal of the toothpick with an endoscope[1] as well as removal with drainage at laparotomy have been described. In our case, the choice of treatment was made before diagnosis of the toothpick perforation. The site of perforation did require closure.

Summary

A case involving intestinal perforation by a toothpick is presented. Although toothpick perforations of the gastrointestinal tract are uncommon, a high index of suspicion must be maintained, especially if the person who presents with obscure abdominal complaints wears dentures; these people are most likely to experience accidental ingestion of foreign bodies. Because a patient rarely realizes that he has ingested a toothpick and because the symptoms of perforation closely resemble those of more common intra-abdominal disorders, a correct diagnosis before surgical operation is difficult to make. In our case, the toothpick was discovered only after doing a gastric resection for presumed perforation of an atypical duodenal ulcer.

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Orthodox Medicine Humanistic Medicine Holistic Health Care

BEGINNING IN THE December 1979 issue the editors of THE WESTERN JOURNAL OF MEDICINE began a forum for dialogue and discussion of orthodox medicine, humanistic medicine and holistic health care. The forum was initiated with statements by persons known to have an interest in and knowledge of this subject. Readers are invited to submit their views constructively and succinctly. As many as space permits will be published in future issues of the journal. At an appropriate time all of the material, published and unpublished, will be collated and, if possible, a distillate will be prepared to summarize the dialogue and discussion.

—MSMW

The Scientific Marketplace and the Medical Establishment

ROBERT H. MOSER, MD

AS ALWAYS, I admire the sense of fairness and adventure of THE WESTERN JOURNAL OF MEDICINE, but I think this present forum is ill-advised. It affords unjustified publicity to the "holistic movement."

I was especially irritated by the article by Rick J. Carlson ("Holism and Reductionism as Perspectives in Medicine and Patient Care") in the December issue. How dare he say such things as

> Holistic thinking, as an epistemological notion, requires that human beings be perceived as whole persons made up of physiological, emotional, intellectual and spiritual dimensions that dynamically interact, and that any approach to improving the health of human beings, either individually or in groups, requires placing them in a larger and richer context *than does traditional medicine.* (Italics mine.)

Dr. Moser is a medical executive, writer and teacher in Philadelphia.

Refer to: Moser RH: The scientific marketplace and the medical establishment, *In* Orthodox medicine, humanistic medicine and holistic health care—A forum. West J Med 132:160-161, Feb 1980

Where are the data indicating that physicians do not consider the "physiological, emotional, intellectual and spiritual" (and the cultural, nutritional, economic and environmental) factors that are concerned in well-being?

We *traditionalists* stand on a few hundred years, at least, of tough, marketplace, hard-bitten experience with patients. In the past what *worked,* survived; what did not work, failed. Physicians made a lot of mistakes. But we do better every year. We developed a thing called the *scientific method,* and we of the Establishment are all that stand between the innocent *consumer* and the hordes of would-be healers who hover outside the gates ready to swarm the medical marketplace. We can advise these *consumers* when they are about to *consume* our product—medical care. We are obligated to warn them about the charlatans, jugglers, holists and anyone else who offer *alternative methods.* Alternative to what? Alternative to hard-won peer-reviewed, double-checked medical experience that has withstood the test of the scientific marketplace. What we offer represents the current top-of-the-line in care. It may be (and probably will be) superseded by some new tests or procedures or medications that prove—again by competing in the tough marketplace of medical science—that they are better than what exists. This is the crucible of scientific medicine. It is not perfect, but it is the best system yet devised.

So I say the following to Mr. Carlson and all of his would be healers: "Lay it on the line. Prove it. Let it stand the acid test of tough, steely-eyed, impartial testing and retesting via the scientific method. If what you have is good, if it really works, God bless you; the Establishment will embrace you and welcome your method. We may not understand how it works (that will come later), but if you can prove that it works, and that it is better than what we are using, it will be welcomed with open arms and brass bands."

I cannot object too strongly when someone stands back and professes that we of the Establishment care little about the social, environmental, nutritional, cultural or spiritual well-being of our patients. You bet we care—and so do priests and politicians. But we can go them a step further: we can bolster the failing heart, eradicate the invading pneumococci, cut out the brain tumor, diagnose and help the depressed patient. We can console the dying, refurbish the malnourished and succor the bereaved. But we can also treat (most often) the sick organ within that sick patient. We

have been doing it for generations and we are getting better at it all the time. And that is why we are the Establishment.

The paper by James Vargiu and Naomi Remen ("What Is Health For—Human Priorities in Health Care"), also in the December issue, had more substance. However, the idea is not new. Virtually every day clinicians face the problem of dealing with patients in the total context of their environment and life-style, often making compromises with *optimal* care to meet the peculiar demands or the situation or the patient. In combat—perhaps the cardinal example—medical officers are obliged to make many medical compromises in order to keep soldiers in condition to meet the impossible demands of warfare. Physicians working with athletes in a game or attending statesmen at a major international conference, or businessmen at a key board meeting, face the same issue of keeping the patients functioning within the circumstances and environment—often at the cost of some compromise with ideal methods of management.

These are short-term situations, but much the same thing occurs in long-term management. How does one deal with patients with chronic obstructive airways disease who continue to smoke, or alcoholic patients who cannot seem to stop drinking, or other sick patients who abuse themselves through lack of intellectual discipline or because of emotional instability—which are often anathema to the physician. Yet such persons stand in dire need of our support and service. One does not desert such patients. The physician attempts to do his best to keep the patient functioning, for as long as possible. *Quality of life* has entered the equation; it stands beside survival.

As I have written in other places, the patient is the captain of his body and soul; he may opt for the disciplined life (diet, exercise, avoidance of *unhealthful* habits—which can represent a sterile, unacceptable life-style for many) or he may elect the *short but happy* life, taking advantage of all the pleasures of body and spirit, enjoying every hour, willing to accept less time but utilizing it to the fullest. Who is to say who is wrong? And a physician who becomes judgmental is in the wrong business. A physician may elect to avoid having responsibility for the patient who abuses his body or tortures his mind, but it always must be placed in the total context of our mission, as physicians to patients.

Holistic Medicine—A Personal Approach

T. E. CLEAVER, MD

THE INITIATION of this forum is a good thing. I believe it will permit interested physicians to develop an overview of the apparently divergent techniques rampant in the holistic concept, and perhaps to generate a commitment to those attitudes and methods that appeal to them. Important to these doctors is the exposure to their doubting peers of the possibility that not only are these subjects not a threat when used with discretion (whether or not they ultimately prove reliable), but that many are, to a greater or lesser degree, currently part of the practice of most of us.[1] There is general agreement, certainly, that each person has a responsibility for his own well being, and in some ways is accountable for his disease.[2] Well-accepted categories of advice about disease prevention common to orthodox and holistic practices regard diet, exercise and rest. In addition, the rediscovery of techniques of conscious relaxation are being carefully reevaluated.[3,4] Methods farther out than these await a consensus.

Look for example at general dietary advice. Much of the chaff of the reductionism of yesterday's incomplete knowledge is blowing away, leaving reasonably simple and common sense kernels, which are generally agreed on and, importantly, digestible by the people. Seldom must advice be more complicated than the following: stay as lean as possible consistent with feeling well, eat a variety of grains, fruits and vegetables (the fresher the better), permit meat in small amounts and avoid salt, saturated fats and excess carbohydrates. To this, the "holist" might add how, why and when to eat, recognizing the benefits of chewing food to water before swallowing, of cooking and serving it with love and beauty, and of avoiding food when disturbed. Perhaps orthodox physicians might draw the line here, not entering the realm of fasting, herbs and fad diets because little of this is of "scientific value." Although, in general, I would agree, consider the following:

Dr. Cleaver is in the private practice of internal medicine, Mount Shasta, California.

Refer to: Cleaver TE: Holistic medicine—A personal approach. *In* Orthodox medicine, humanistic medicine and holistic health care—A forum. West J Med 132:161-163, Feb 1980

- A short-term fast rarely causes harm; herbs are a country tradition everywhere and often do help.
- "Scientifically proved" implies that somebody wants to study the matter, knows how and has—and that the current scientific community is interested in the results.
- The act of commitment to diet is a mental focus on change for the better, on taking control, which is something very different from placebo effect, and infinitely more difficult to study.

Shall we do nothing while waiting for information from a cumbersome scientific system? I think it is fun to dispense pennyroyal tea occasionally as a sedative—it beats the standard drugs in cost and safety, and people love it (the act and the tea), especially the elderly. I want to be tuned in to inappropriate practices as well, such as vitamin A deficiency in extreme macrobiotic diets, and herbal intoxications.[5]

I do not advocate that the thoughtful healer swallow whole any method that is absurd to him, including the attached references. Instead let the incisiveness of his training support the inquisitiveness which leads him to read this paper, looking at methods new to him, honoring the antiquity of some, and selecting aspects useful to his practice rather than opposing a technique simply because he does not yet understand it. Recognize good teaching wherever it may be found and carefully extract only that which is useful.[6,7]

Exercise which is regular and physically demanding (for Americans) over a protracted time, such as an hour, must be carefully prescribed on an individual basis, all practitioners agree. It really does not matter whether the resulting euphoria and physical improvement is the result of autonomic impulses or the act of taking time to improve oneself. It is the attitude of the healer and client toward what they do that makes the difference between seeing healing as something from outside the client, or an act of will for which the client takes full responsibility and credit.[8,9]

Grandma knows the value of rest. But more than a good night's sleep seems necessary. Americans are either on the go or asleep. Ask about relaxing and you will hear about books, knitting, gossip, beer and other *busy-ness,* but not about relaxing, except, perhaps, a nap. Of course, none of that is wrong, but it is incomplete—it cannot balance for most people the tensions inherent in our way of life. We are learning the benefits of practicing relaxation formally[10] in order to discover how it feels and how it can be taken into life and used to prevent the stress response.[11] It does not seem to matter what gimmick is used, whether biofeedback, autohypnosis, transcendental meditation, hatha yoga or simply controlled daydreaming. It is the act of doing it regularly that results in positive physical and mental change[12]—taking time to concentrate on doing *nothing* well, paradoxically achieving wellness in the world by the very act of letting go of the world without becoming unconscious (asleep).

It is important to look at the history of orthodox medicine for clarity in reviewing new or rediscovered methodologies. Each practitioner must ask himself how many times his own advice and drugs of yesterday are silly or harmful today. We have fought an organization only to lose repeatedly. We have accepted and merged with another only to win. Why must we be put off by chiropractic theories that appear to be nonsense, when in selected cases we can see quick and excellent results? Why snort at Bach flower remedies (a system of treatment using flower extracts) when they are probably harmless and may produce prompt results? Who is now willing to pan acupuncture, acupressure, and jin shin jiutsu when trigger points are already part of our tradition?[13]

The primary trap that practitioners of these specialties fall into is the same one that traditional medical persons are heir to. We all have a method to sell. We see it work for many and sincerely want it to work for all. The form of the trap is not only complacency and ignorance, but not paying attention to that brief intuitive spark that sounds an alarm to look deeper into a particular patient's condition. It is found in the physician who does not refer appropriately just as in the new-age healer who puts an insulin-dependent diabetic on a lemon juice and molasses fast, collects his fee and leaves town. This is the negative side of the precise reason why physicians need to be conversant with new methods, if for no other reason than by default, no one else in town has the background, ethics or tolerance to fairly present to patients the *big picture.* It is a no-lose situation, Doctor: your ego is fed by allowing you improved powers of consultation; the good ancillary practitioners are blessed and educated by your open lines of communication, the bad ones are identified by *their* peers; public trust in the medical profession is bolstered, and

perhaps your work load is lightened. There is harmony instead of competition. And together, physicians and people accelerate the national urge toward learning methods that are client oriented, not healer dependent.

This in turn accentuates wellness (prevention) rather than cure, emphasizing that a person can learn the enormous power that he can exert over his physical and mental evolution, an attitude surprisingly foreign to our social structure. This does not threaten you, it relieves you.

All techniques work on some people some of the time. But on whom and when? Consider that each method can be effective, even Laetrile and psychosurgery in a selected person because that is the moment he has prepared for and earned good results from in some way and *he is at last ready for change.* This is no more (or less) mysterious than a truly sick patient who finally finds the right physician and is well with hardly any treatment. Each new technique may be simply a special application of time spent concentrating (meditating) on wellness.

An exhortation: learn from those trying to practice these new arts. They are likely to be young, especially in experience; forgive their intolerance, teach them the "and" of maturity ("I choose this *and* this") rather than the "either—or" of youth ("I must choose *either* this method *or* that one"). Point out to them that you have spent a lifetime cultivating a sense of holism that enables people to prevent disease by diet, exercise and rest; that you provide the information that helps some patients turn against chemotherapy; that you give patients the opportunity to face death if they wish,[14] and that you offer traditional medicine, which is what they thought they came for, when it is appropriate but not before.[15]

It is difficult to understand the resistance, resembling at times fear, of so many doctors to the spiritual aspect of their practices. They take an oath given by one of the great priest-physicians, who practiced in a temple and used dream interpretation.[16] They are moved to tears by the love they see. They enjoy doing good. Why do they forget that the separation of priest and physician is much clearer in their minds than in their patients? They should be more willing to *lose* their minds—much of what we do is "mindless" anyway, occurring on a feeling level. To open the door to feelings a bit wider is to balance our science.

Let us examine how we really operate. Consider the usual new patient. Within an extraordinarily brief time an experienced physician has an intuitive flash (a mystery to a new medical school graduate), then restricts his subsequent examination to *scientifically* proving that intuition. Now, perhaps *intuition* is simply a mixture of training, experience and what the doctor read last night. I believe there is something more, a *reading* of the patient, a productive line of questioning that at times follows no logic, knowing without knowing how.

This is the kind of sensitivity that is the greatest potential gift of an individual healer, the kind that can be offered by a good friend. It permits the examiner of a patient with a sore throat or a backache to ask "What's going on at home?", opening a Pandora's box of disasters which with skillful listening the physician can use to help the patient get on with problem solving.

Physicians, like it or not, are already practicing even the most occult of holistic arts to some degree, and have been doing so for millenia.[17] We might as well be conscious of what we are doing. The techniques may need study,[18] expansion and refining; ancillary personnel must be accepted because of time constraints; more emphasis is needed on prevention, reassuring the patient that he has control if he chooses—but the fundamental caring and ability to touch lives without fear are already in place.[19,20]

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

An Antiabortion Viewpoint

To the Editor: I read the recent article by Dr. Malcolm Potts about abortion (Potts M: Changing attitudes toward abortion, pp 455-462, Nov 1979) with shame and embarrassment. I was shocked that the Western Journal would print an article that so obviously misrepresents the antiabortion viewpoint.

In the first place, no one is arguing that the Supreme Court decision "invented" abortion. The issue is, and has been, whether the act of abortion is right or wrong. Dr. Potts' rather long effort to demonstrate that abortion was widely practiced and at times generally accepted in the past is, therefore, really beside the issue. It does not logically follow from such a demonstration that there is no right or wrong decision concerning abortion, it merely follows that opinions have varied and probably will continue to vary. The argument, that because there is an observed variance of opinion on this matter there can be no right or wrong position, is exactly analogous to saying that because there is a variance of opinion concerning whether the world is flat or round or some other shape (as was the case in the time of Columbus), there can be no right or wrong concept about the shape of the world. This type of reasoning, whether applied to the shape of the world, abortion or any other issue, makes no sense at all.

Second, Dr. Potts accuses the antiabortion position of offering simple solutions to complex problems and of forgetting the "brutal realities" of poverty and fertility regulation. In reality it is the abortionists who are offering the simple solutions. In the article the strong implication is that abortion is a useful and reasonable tool in dealing with the problems of poverty and overpopulation. This, to me, is the simple solution. Quite to the contrary, the antiabortion position holds that abortion results in the taking of a human life and that this human life is extremely valuable, more valuable than mere money or affluence. This high view of human life compels us to seek other solutions, however difficult and costly, to the problems of poverty and overpopulation, rather than attempting to stamp out poverty by stamping out the poor.

Finally, the antiabortion viewpoint is represented as misinterpreting the Supreme Court decision on abortion. Again, I think the situation is exactly the opposite. The Supreme Court decision in effect stated that prior to some vague point of viability the human fetus cannot come under the protection of the law granted to all persons by the 14th Amendment to the Constitution. It is this abnormal, fragmented and arbitrary concept of human life that the antiabortion viewpoint opposes. Those opposed to abortion contend that there is no compelling biological, legal or ethical reason to link human value or personhood with a vague concept of viability, size or organ development. Furthermore, the antiabortion view points out that from a strict biological perspective it can only be concluded that human life begins at the moment of fertilization and not at some mystical 20 to 22 weeks of gestational age. With these considerations in mind, it can be seen that the Supreme Court decision is in error because it ignores at best, and contradicts at worst, the available, rational evidence that significant, valuable human life begins at and continues on from the moment of fertilization. Consequently, those who fail to perceive the deep and dangerous blow that the 1973 decision on abortion dealt to our concept of humanness, are the ones who misunderstand the true meaning of the decision.

How shameful it is that we as a profession are attempting to solve deep-rooted problems at the expense of the most innocent, helpless and de-

fenseless members of the human race. As physicians dedicated and trained to preserve human life, we should not apathetically sit by and allow our profession to accept the miserable role of social executioner.

DALE JOHN STRAWN, MD
Visalia, California

On Refrigerating Unused Pitressin Tannate in Oil

To the Editor: In "The Clinical Physiology of Water Metabolism—Part II" (November 1979), the authors, in discussing the treatment of diabetes insipidus, suggest that unused portions of Pitressin Tannate in Oil may be stored in the refrigerator. Although not stated in the package insert provided by Parke, Davis & Co., this preparation of vasopressin suspended in peanut oil should not be refrigerated. Refrigeration will cause a reduction in solubility with precipitation or crystallization of the ingredients.[1] I would also question the practice of saving the remaining contents of a single-use ampule since the formulation does not contain a preservative.

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REFERENCE

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* * *

Dr. Kleeman Replies

To the Editor: The authors appreciate the comments of Dr. Kikugawa. Pitressin Tannate in Oil is used far less frequently today in the treatment of diabetes insipidus because of the availability of preparations that are simpler and more practical to administer. We were unaware of the effect of refrigeration, and we agree completely with her comments.

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Why Mandatory CPR?

To the Editor: At the latest California Medical Association-California Hospital Association Audit Workshop, our team demonstrated a quality of care study on "Code Blue." Its objective was to improve staff performance in cardiopulmonary resuscitation. According to documentation in the medical record flow sheets, our doctors, nurses and hospital support system were functioning very well indeed. But so much for process criteria; what about outcome? Results were dismal: only 33 percent of patients survived cardiopulmonary resucitation (CPR) and a bare 11 percent left the hospital alive.

These figures are reflected in studies from other hospitals, large and small, with or without coronary care units, emergency rooms or cardiologists. Even with intensive care, the CPR salvage seems to depend more on underlying diseases than on the best staff efforts to respond. Evidently here is an example of statistically unrelated process and outcome, or the possibility of an undeveloped "code-no code" policy.

Yet the Joint Commission on Accreditation of Hospitals' (JCAH) standard on continuing medical education requires that all staff doctors "have participated in basic CPR training and are considered so qualified." When our education committee wrote to the JCAH about this, the answer made two points: even if CPR is a rare event, wherever it happens, all doctors should know the ABC's of sustaining life; and "a CPR requirement was established because there is an identifiable need to enhance the quality of this particular aspect of care." The *AMA News* also produced a poll showing that doctors by and large had approved of this universal requirement for hospital staff appointment.

Consequently the California Medical Association endorsed this concept, hospital staff bylaws adopted it as a biennial mandate and now from one to four hours per physician are expended meeting this continuing medical education need—approved, it is to be hoped, for Category 1 credits. For our medical staff this amounts to about 300 professional hours a year, time away from patients. However, studies continue to show that special CPR teams get to all Code Blues, that doctors do not carry out CPR anywhere else and that CPR survival in hospital has not significantly changed. Or did we miss some data?

So is it not about time, before more good intentions become staff requirements, for this continuing medical education to be scientifically evaluated? At least it would guide us in the amount and kind of CPR best for physicians to know, rather than the usual overtraining recommended.

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Sacramento, California

Special Article

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The New Quality Assurance Standard of the Joint Commission on Accreditation of Hospitals

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The Joint Commission on Accreditation of Hospitals (JCAH) has continuously emphasized improvement in the quality of care provided in hospitals as the central purpose of the accreditation process. In striving to assure such improvement, the JCAH has stressed the need for, and the responsibility of, the medical and other professional staffs to provide continuing review and evaluation of patient care. In recent years, quality assessment activities have evolved, proliferated and matured to the extent that they require a purposeful integration if they are to effect sustained improvement in patient care and clinical performance. To assist hospitals in the coordination or integration of quality assessment activities, the Board of Commissioners of the JCAH has approved an important new quality assurance standard.

Significant requirements of the new standard are a comprehensive quality assurance program, a written plan, a problem-focused approach to the review and evaluation of patient care and clinical performance, an annual reassessment of the program, and an improvement in patient care or clinical performance. The new standard reflects the JCAH belief that an integrated, problem-focused approach to quality assurance will significantly improve the quality of care provided throughout a hospital. Such an approach recognizes the interdependence of hospital departments and services in the provision of patient care, and, therefore, requires a purposeful integration or coordination of quality assessment data and activities. Consequently, quality assessment data may be utilized effectively and efficiently, and many potentially useless or duplicative quality assessment activities can be eliminated. The new standard affords hospitals considerable flexibility in the manner in which they implement and administer the program and encourages innovation.

IN AN EFFORT to upgrade the level of care provided to patients in this country, hospitals and organized health programs voluntarily participate in surveys conducted by the Joint Commission on Accreditation of Hospitals (JCAH). These surveys, which are based on standards representing a broad-based, consensus approach to quality assurance, focus on the organized efforts of a

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hospital's authorities and staff to assure the provision of quality medical care and on the physical safety of the facility's buildings and grounds.

When the JCAH was formed in 1951, its initial efforts were aimed at establishing and maintaining "minimal standards" for patient care. During the 1970's, however, the emphasis has shifted to attainment of the "optimal achievable" in care provided. To meet this goal, the JCAH develops and revises standards based on "an identifiable need to measure or enhance the quality of a particular aspect of care or service."[1] These standards have certain characteristics: "They are valid, that is, they relate to the quality of care or services provided; they are optimal, reflecting the highest state of the art; they are achievable, meaning that compliance with them has been demonstrated in an existing facility; and, compliance with them is measurable."[1]

The standards, of course, are useful only to the extent that health care institutions utilize them appropriately in self-study and that JCAH surveyors apply them in accreditation visits. Furthermore, accreditation indicates that a health care facility has the capability to provide quality care and that this capability was documented during the course of the survey and consultation process. Both providers and consumers who utilize accreditation as a reference for selecting hospitals must understand this important distinction.

Evolution of Quality Assurance

Throughout its history, the JCAH has encouraged multiple approaches to the review and evaluation of patient care provided in hospitals and other health care facilities. Until the late 1960's, accreditation surveys focused on hospital board organization and functions, medical staff membership and organization, qualifications of other health care personnel, effectiveness of support services, and completeness and accuracy of medical records. Surveyors, through their discussions with hospital staff members and their examinations of selected medical records and committee minutes, gained insight into certain aspects of patient care. Their ability to secure an overall picture of the outcome of that care, however, was limited.

With the advent of the 1970's, business, industry, government agencies and third-party payors became increasingly concerned about both the utilization and quality of services provided by health care facilities. In accordance with the growing movement toward continuing education, utilization review and cost effectiveness, the JCAH began to strengthen measures for quality assessment. In 1972 the JCAH presented the assessment model later called PEP (the Performance Evaluation Procedure for Auditing and Improving Patient Care), or "audit." John D. Porterfield, MD, then director of the JCAH, defined audit as follows: "It is oriented toward outcomes, uses the screening and pattern technique with specific criteria, analyzes the cause of clinically unjustified variations, proposes the remedy and deals in units that anticipate not large but specific change."[2] Audits were expected to provide results for structuring continuing education programs, delineating clinical privileges, and improving use of staff and resources. A few audit proponents even claimed that audit would negate the need for review committees (such as tissue, antibiotic, blood, and medical record committees). Experience quickly showed these committees would continue to be needed.

To ensure use of the audit methodology in review of patient care, the JCAH established an audit requirement and later specified the number of audits to be completed annually. The federal Professional Standards Review Organization (PSRO) program subsequently agreed to adopt similar numerical requirements and avoid duplicative or conflicting requirements.

New Directions in Quality Assurance

Although the objectives of audit are desirable and many hospital staffs have successfully completed audits that have been useful in analyzing patterns of care and in educating practitioners, audit has often been regarded by physicians as tedious, costly and nonproductive. Efforts to meet audit requirements have too frequently been a matter of paper compliance, with heavy emphasis on data collection and few results that can be used for follow-up activities. In the shuffle of paperwork, hospitals often lost sight of the purpose of the evaluation study and, most important, whether change or improvement occurred as a result of audit.

Following survey findings and research that indicated that patient care and clinical performance had not improved to the extent anticipated, the Board of Commissioners of the JCAH in 1978 directed staff to examine alternative methods for assessing the quality of care in hospital settings. After an extensive review of the literature and

discussion with many professionals involved in quality assessment activities across the country, a broadened approach to quality assurance was proposed. A new standard was developed and tested, and then approved by the Board of Commissioners in April 1979, with the understanding that there would be sufficient lead time before its application to the accreditation decision process. This will allow the JCAH to complete training of surveyors and orientation of hospital staffs and give hospitals an opportunity to begin coordinating existing review and evaluation activities. The standard, which was published in the 1980 edition of the *Accreditation Manual for Hospitals* released in August 1979, will be used by the surveyors for consultation purposes until it becomes effective for accreditation decision purposes on January 1, 1981.

In addition to approving the new quality assurance standard, the Board of Commissioners of the JCAH also eliminated the numerical requirement for patient care audits, effective April 1979. This does not imply any lessening of interest or support of audit as a valuable tool for evaluating patient care. Rather it reflects a shift from an emphasis on numerical requirements to a broader and more flexible approach to quality assurance that includes audit as a more comprehensive quality assurance program.

Elements of the New Quality Assurance Standard

The primary aim of the new quality assurance standard is to shift emphasis from method to results, from diagnosis-specific audits to hospital-wide, problem-focused reviews that build on current hospital activities and strengthen the coordination and integration of overall quality assurance activities. Audit, without the associated numerical requirements, remains a recognized and useful assessment tool, but now should be coordinated with other appraisal tools that can be used to solve identified problems in patient care and clinical performance.

By giving hospital staffs more flexibility in the selection and identification of problem areas and in the performance of studies in these areas, the JCAH believes that both the study process and results will have greater impact on patient care. In keeping with this approach, the JCAH will examine the following elements of the new standard to verify the effectiveness of quality assurance programs:

- The integration or coordination of all quality assurance activities into a comprehensive program;
- A written plan for the program;
- A problem-focused approach to review;
- Annual reassessment of the program, and
- Measurable improvement in patient care or clinical performance.

Integration or Coordination of All Quality Assurance Activities

The intent of the new standard is to preserve and expand the variety of effective quality review efforts being carried out in the hospitals by physicians, nurses and allied health professionals. The new standard is also intended to encourage productive interrelationships and coordinated efforts so that duplication of activities will be minimized; planning and communication will be enhanced, both in execution of studies and in follow-up of results; and costs and paperwork involved in completing the studies will be reduced.

In an effort to improve care in their individual departments, the professional disciplines in many hospitals had developed their own separate studies. Except through informal communication, no means existed for coordinating and linking these studies or for ensuring that corrective actions would be implemented throughout the facility. The new standard will offer hospitals the opportunity to utilize staff and resources more effectively in carrying out quality assurance efforts.

The JCAH believes that hospitals will welcome the idea of integrating or coordinating quality assurance activities into a single, comprehensive program. In larger medical centers with large, almost autonomous departments, problems with integration or coordination may occur. Surveyors will need to recognize the problems of these large departments and help hospital managers develop ways of coordinating activities.

In using the new standard, hospitals will continue to rely on the medical record as a major source of information for problem-related studies, but they will have wider latitude in choosing other problem-identification sources related to patient care. These sources could include morbidity-mortality studies; monitoring activities (medical and other professional staffs); findings of hospital committees; review of prescriptions; hospital profile data (PSRO and other regional data); process and outcome studies; incident reports (safety and clinical care); review of laboratory, radiologic

and other diagnostic reports; financial data (hospital charge data and liability claims); utilization review findings; staff interviews; patient surveys and comments; and data from third-party payors.

Written Plan

For its own use as well as that of the surveyors, a hospital will be required to have a written plan describing the overall organization of the quality assurance program. The written plan should answer these questions: Who has responsibility for the overall management of the quality assurance program? Who is accountable for determining that meaningful problem-focused studies are carried out and the results communicated in a timely fashion to appropriate medical and other health care professional staff and to management and the governing board? What methods will the hospital use to ascertain that its quality assurance program is being utilized effectively to examine problem areas that touch on all services and health care personnel? What methods will the hospital use to determine annually that its quality assurance program is consistent with its written plan and comprehensive enough to assure that identified problems in patient care are being studied and effectively resolved? If the hospital is now meeting JCAH quality assurance requirements, developing and implementing the written plan should not require additional personnel. Several of the hospitals that participated in the developmental stage of the new standard identified a person or committee (or both) within their current organization who, with some modification of responsibilities, could supervise and carry out the new approach. They speculated that costs incurred in implementing the written plan would be minimal, compared with benefits gained through the new approach, and that credit would now be given to continuing patient care review activities previously not recognized in an accreditation survey.

Problem-Focused Approach

The advantage of the audit methodology, with its retrospective focus, is that it looks at the results of diagnostic-specific treatment or therapy processes by analyzing patterns or developing data profiles. Carefully developed and completed studies are quite useful in helping practitioners examine patient care problems and are especially helpful in designing educational efforts to change practice patterns. The new standard not only recognizes the value of audit for those who use it, but also recognizes the value of other methods of review to effect changes in future health care services.

The new standard requires a basic, problem-solving approach: First, problems must be identified and priorities for problem-solving established. What problems does a hospital want to study and why? Second, which of the problems listed are most important or critical to improving or maintaining quality of care, and which will have the most benefit in terms of dollars or effort expended? In other words, the standard helps in setting priorities. Third, what are the dimensions of the problems? Can they be studied, and do they touch upon major services and practitioners? Are resources available to resolve these problems? Fourth, what are the sources of criteria? If they are to be valid benchmarks against which to measure results, should they be developed locally or adapted from standards of practice established by professional organizations or research studies? Finally, what actions should be taken to resolve the problems?

Measurable Improvement

The review process will not be considered complete unless steps are taken to implement and follow up corrective action. The use of a basic problem-solving approach that utilizes multiple sources for identifying problems adds to a hospital's flexibility in resolving problems. Problem resolution may include development of specific education programs on given procedures and verification that staff benefited from these programs. Medical staff privileges or functions of other health care personnel may be more carefully defined, limited or enlarged under certain conditions. Policies or procedures may be changed or staffing reallocated to bring about higher quality performance. Through various committees, the results of these actions can then be monitored to determine whether the problem was actually corrected or if it reappeared in several months.

Communication of Results

One of the obvious voids in quality assurance programs has been the lack of understanding of the quality assurance effort on the part of hospital management and governing boards. In many settings, quality assurance activities have been delegated to medical staff with some help from nursing and medical records. The language of audit was

sometimes mystifying, and results reported in medical terms did little to capture the interest of management and governing authorities.

Given the increasing scrutiny of the quality of practitioner performance by outside agencies, the attention to risk management concerns and the growing emphasis on cost-effectiveness, hospital administrators and governing boards need to take greater interest in quality assurance efforts, results and benefits. The JCAH believes that by making assessment requirements more flexible and by expanding problem solving to areas other than patient diagnosis and treatment, interest and communication on the part of management and governing authorities will be strengthened because they will now be able to suggest and observe the study of problems that they believe are in need of resolution.

Relationship Between the New Standard and AMH Requirements and Accreditation Status

The new standard is designed to complement the other statements related to quality and appropriateness of services found in the *Accreditation Manual for Hospitals*. This is consistent with the JCAH's goal of enabling hospitals to integrate review of all care provided, not just a small portion of it.

Commentary

Although the process of providing greater latitude to hospitals in conducting studies of patient care seems simple, the JCAH is receiving requests for both more detailed definitions of documentation acceptable to surveyors as well as assurance that surveyors will be flexible in their review of evaluation studies. Some of those who have submitted queries have expressed a preference for formulas or models to guide them.

Until the formal implementation of the new standard on January 1, 1981, surveyors will continue to review hospital quality assurance programs and will provide consultative assistance. To encourage innovativeness and flexibility in devising comprehensive quality assurance programs, JCAH surveyors and education programs will present model programs designed to aid hospitals in developing organizational structures and procedures for implementing the quality assurance program that will be most beneficial to patient care.

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A Caveat

REMEMBER, the fact that the patient has significant organic disease, either of the nervous system or elsewhere, does not mean that he does not have hysterical disease as well. The two disorders can coexist. . . . I have seen, in the past couple of years, three or four patients who went into coma and who were seriously ill. The coma occurred because they were psychologically incapable of dealing with their organic illness by any other defense mechanisms. So a variety of psychological illnesses can cause coma.

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Nurse Practitioner and Physician's Assistant Clinics in Rural California

Part I: Issues

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The primary health care needs of at least 26 rural California communities are being served by nurse practitioners (NP's) or physician's assistants (PA's). All of these have physician supervision and support. NP's and PA's have proved to be acceptable and effective. With 230 rural areas in California identified as having unmet health care needs, this type of service is likely to increase and should be supported.

NP/PA clinics serve total populations or concentrate on Indians, Chicanos or the poor. Many barriers have been overcome, especially over the past four years, to allow these clinics to flourish and increase in number. The availability of nurse practitioners and physician's assistants has increased due to support to schools and to school policies. Clinic funding has greatly improved; federal funds for general rural clinics, Indians, migrants, family planning and maternal-child health have been greatly supplemented by California state funds. Beginning in 1978, rural NP and PA services can be reimbursed by Medicare and Medi-Cal (California's Medicaid program).

Since 1975 state laws have defined PA and NP roles broadly, and these roles are more precisely defined at the local level. Although nurse practitioners and physician's assistants generally cannot prescribe or dispense drugs (a major problem in many clinics), demonstration legislation allows special pilot projects to do both. As remaining funding and legal problems are corrected, NP's and PA's will serve an even greater role in rural areas.

MANY RURAL AREAS throughout the nation have inadequate health care. In California, 230 rural areas needed additional medical services as of June 1978, according to the Health Manpower Policy Commission.[1] Some areas are too sparsely populated to support a physician. Other areas could support a physician, but physicians prefer to locate near hospitals, usually in larger towns.

Nurse practitioners (NP's) and physician's assistants (PA's), supervised by physicians in nearby towns, could meet the needs of many of these areas. Though the idea of NP/PA clinics has been proposed for years, only eight such endeavors

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have been reported in the United States outside of California according to MEDLARS listings over the past seven years. These have been in Vermont,[2] Florida,[3,4] Kentucky,[5,6] Idaho,[7] Nebraska,[8] New Mexico,[9-12] Washington state[13] and Oklahoma.[14]

The implementation of the NP/PA model has been hampered by many obstacles including the following.

- Consumer-related issues:
  Unclear documentation of local need,
  Anticipated lack of patient acceptance.
- Provider-related issues:
  Unavailability of NP's and PA's,
  Problems in defining and providing adequate physician supervision,
  Difficulty in developing adequate physician-NP/PA teams, especially when members are remote from each other,
  Weak support systems such as laboratory, x-ray and pharmacy services, and
  Uncertain or unavailable professional liability insurance for NP's and PA's.
- Financial issues:
  Inadequate capital and support funding, and
  Sanctions against NP and PA reimbursement by public fee-for-service programs.
- Legal issues:
  Unclear or restrictive legal roles and definitions of NP's and PA's,
  Legal sanctions against NP's and PA's prescribing drugs, and
  Legal sanctions against NP's and PA's dispensing drugs.

Changes and breakthroughs, especially between 1975 and 1978, have affected all of these areas. Legislative attempts to deal with certain problems have transformed some from obstacles to positive resources. The changes have encouraged a flurry of NP/PA clinics to open, although not without considerable difficulty. Because this form of medical care is becoming more widespread, it is important to understand how these clinics function. Each of the issues given above will be discussed, including its current status in California as of April 1979.

Methods

The authors identified clinics operated by NP's and PA's from lists provided by five California NP and PA schools, the National Health Service Corps (NHSC), the California Division of Rural Health and by word of mouth. We contacted each of these facilities and, in most cases, nurse practitioners or physician's assistants as well as administrators were queried. We asked about the operation of the clinics and how each of the problems in our outline was being handled.

Finally, relevant laws, administrative guidelines, and agency internal reports were studied to ascertain operational procedures, current numerical impact and anticipated changes.

Findings

Consumer-Related Issues

Unclear documentation of local need. Populations in remote towns use health care services less frequently than populations in towns nearer the source of that care.[15] A patient's ability to travel to a physician involves, in part, the distance, road conditions, and availability of public transportation and time.

The California Health Manpower Policy Commission defined 230 rural areas with unmet needs, using census tracts with ratios of population to primary care physicians of 1,855 to 1 (or lower, given certain conditions).[1] Federal criteria are stricter, listing 28 rural manpower shortage "rational service areas," using a 3,500 to 1 base, but with mortality and population considerations, including ethnicity.[16]

Differing needs are expressed by certain population subgroups who cannot readily use local resources. The poor may not be able to afford private care. Many Medicaid (known in California as Medi-Cal) recipients state that they are unable to find physicians who will accept that program. Finally, some ethnic groups have special needs due to differences in language and culture. The definition and quantification of poverty and ethnic group needs are highly problematic, and social policy regarding them is controversial. Many of the NP/PA clinics in our survey were established specifically to serve these subgroups.

Need is most often defined and voiced by people who feel that need—these same people often organize, explore resources and set up a clinic. The number of patients needed to justify such a facility depends on availability of subsidies. Some clinics serve very few patients, but are subsidized because alternative sources of care for those patients are not deemed adequate by supporting agencies.

Anticipated lack of patient acceptance. According to two studies, rural populations which have

not used the services of NP's[17] or PA's[18] have limited acceptance of the idea. They have considerable reservations about which problems they would entrust to NP's and PA's and about availability of physician back-up and supervision.

Many of the clinics in our survey reported a similar history of public resistance to the idea of programs staffed mainly by NP's or PA's. Many towns or clinic boards accepted an NP or PA only when it was obvious that no full-time physician would come.

However, once established, NP's and PA's are well received and highly valued by their patients, according to studies elsewhere.[3,7,8,10,13,14,18-21] Although we found no published studies on surveys of patient acceptance for the California clinics, our data indicate that with a few notable exceptions, patient flow is steady or increasing, with a high percentage of return visits. Patients' doubts and hesitancy, if they exist, apparently can be overcome by good service.

Provider-Related Issues

Unavailability of NP's and PA's. Though NP and PA programs began in the 1960's nationwide, most were small and urban based. California programs began in the early 1970's with classes of under 20 students. The Robert Wood Johnson Foundation's strong support of the Family Nurse Practitioner Program at the University of California, Davis,[22] increased class size to a peak of 96 students in 1976. That school also gave preferential admissions to applicants from health manpower shortage areas. UC, Davis increased decentralized education by establishing classrooms in six rural satellite towns and by using rural physicians as clinical teachers, thus allowing rural students to live at home while learning to meet local needs. The state agreed to continue support as the Johnson Foundation fund tapered. US Health, Education and Welfare (HEW) grants have further helped the University of California at Davis in its NP program, the Foothill College-Stanford University in its Primary Care Associate Program (PA), and the University of California at San Diego to move in a similar direction.

The pool of NP's and PA's selected from and trained for rural California continues to grow. In 1978 to 1979 alone, 238 family nurse practitioners and physician's assistants graduated from nine California schools.[23]

Problems in defining and providing adequate physician supervision. According to well-controlled studies of both process and outcome, NP's and PA's can safely and effectively provide a variety of primary care services.[24,25] NP's and PA's refer 10 percent to 20 percent of their patients to physicians.[3] These studies have been concerned with NP's and PA's practicing in the same facilities as physicians; no studies on quality of care have been reported on NP's or PA's operating at distances from physicians, according to MEDLARS listings since 1971.

The California Physician's Assistant Act[26] and subsequent regulations[27] require that a PA be supervised by a specific physician, approved by the state's Board of Medical Quality Assurance to do so. The physician is to "review . . . either in person or by electronical means, the findings of the patient's history and physical examination and performance . . . on a continuing and timely basis depending on the significance of the findings and the status of the patient." The law does not require that the physician be on site nor does it specify frequency or duration of direct observation.

Similarly, the state's Nurse Practice Act[28] and regulations[29] allow for an extended role including "changes in the treatment regimen according to standardized procedures . . . developed in collaboration with . . . physicians," which shall include a written method for "continuing evaluation of competence . . . [to] specify the scope of supervision required . . . for example, immediate supervision by a physician . . . and [to] specify any specialized circumstances under which the RN is to immediately communicate with a patient's physician. . . ." The law does not require physician supervision nor does it specify frequency of monitoring or methods.

The Federal Rural Health Act of 1978[30] requires visits by a physician at least every two weeks to federally certified rural clinics. Medi-Cal[31] requires that a physician review medical records every week in order for an NP or PA to be reimbursed under that program.

Difficulty in developing adequate physician-NP/PA teams. Rather than working separately, an NP or PA and physician may provide better care by working as a team, each contributing unique insights and skills as well as mutual ones. The California NP and PA schools share this philosophy and build their training programs on physician-NP/PA teams. Many residencies purposefully integrate NP's and PA's into each physician's training so that he or she may experience

the benefits of such a team as well as learn how to be an effective team member.

Physicians and NP's or PA's need to continue to work together to develop the mutual understanding and respect necessary for a collegial team. In satellite situations, however, a physician's involvement is usually through telephone consultations and periodic visits. He or she may see patients with the NP/PA during these visits and may discuss patients previously referred by the NP or PA.

The consensus of participants in our survey was that the team spirit develops well with a minimum of a day a week spent working together. In some instances a physician may be "on the team" who is not the legally designated supervising physician. This difference occurs when a distant agency is administrating a satellite clinic, and physicians nearer are willing to offer medical support to the clinic.

Weak support systems such as laboratory, x-ray and pharmacy services as well as physician consultation other than that of supervising physicians. NP's and PA's need to be introduced to the medical community and their roles explained and accepted in order to insure that all medical services become available to their patients. NP's and PA's need to establish contact with public health, mental health, home health and many other services which may be distant or weak in their support. (Sometimes these services are nonexistent.) Rural clinics can use mail-out laboratory services and receive telephone reports. They can telephone electrocardiographic signals to medical center heart stations and receive immediate reading and consultation services. Some clinics have arranged for medication shuttle services from distant pharmacies. Where certain services do not exist, the clinical judgment of the NP or PA can at least reduce the number of patients who are forced to travel elsewhere to find them.

According to reports given by our survey participants, some laboratory and x-ray services have been refused because they were requested by an NP or PA. More often, there has been good acceptance, particularly where the NP or PA and supervising physician have visited area services to explain their role and to establish contact.

Uncertain or unavailable professional liability insurance for NP's and PA's. Initially, insurance companies did not cover NP's and PA's for malpractice in California. Now two companies insure nurse practitioners and physician's assistants separately when the supervising physician is also a policy holder. The NP or PA is rated the same as the lowest-risk physician categories, and is charged $672 to $800 a year for $500,000 coverage. There is no actuarial basis for this rate.

Three other companies insure NP's and PA's as any other employee of a physician, and are not separately charged.

Clinics may contract for coverage for all their personnel. The charge is based on number of patients seen.

County, state and federal governments cover NP and PA employees in their insurance programs.

Nurse practitioners can purchase separate policies from the California and American Nursing Associations if they are members, at $18 for $250,000 coverage. A private company also insures nurses at a similar rate. However, most physicians' insurance companies cover the physicians' NP/PA employees as a requirement. There is no independent coverage available for physician's assistants.

Financial Issues

Inadequate capital and support funding. Initial clinic cost and continual operating expenses may be met by revenue from patients. However, this source of revenue may not be adequate if (1) the patient flow is too small, (2) patients cannot pay full charges or their insurers do not, or (3) services offered do not generate fee-for-service charges, such as education, social support and outreach. Fortunately, many programs help clinics that are not self-supporting.

Funds may come from local, state and federal sources. Many programs are supported by a combination of federal and state funds which are state administered.

Local funds may come from private investments, gifts, community fund-raising efforts and county taxes, including revenue sharing. However, substantial local funding was rarely available to our surveyed clinics. Investors and banks expect an operation to be self-supporting within a reasonable time. County governments, never well-funded, and worse so since the property tax limitation referendum (Proposition 13, 1978), help only a few clinics, either as an independent effort or as an extension of county health department activities.

Federal funds come mostly through the Rural Health Section, Bureau of Community Service, Region IX of HEW in San Francisco. This office

administers the Rural Health Initiative (RHI) and other programs. The RHI is an effort to coordinate several federal programs, including the National Health Service Corps (NHSC), Community Health Services and Migrant Health.[32] Each program has requirements which must be met by applying clinics. The National Health Service Corps pays the salaries of physicians, NP's and PA's working in the eligible clinics. As of March 1979, 36 clinics in California received some federal rural health funding, 23 had NHSC physicians, and 16 had NP's or PA's, five functioning remote from physicians according to NHSC records.

California provides state funds and personnel through the Rural Health Service Development Act of 1976.[33] This act supplements federal funds, and also supports nonprofit clinics which do not meet federal guidelines. The Rural Health Division of the Department of Health administers the program, which includes the California Health Service Corps (CHSC). As of March 1979, 52 clinics received some direct state funds, 17 had PA's or NP's directly or indirectly funded by CHSC, four remote from physicians, according to a list from the California Rural Health Division.

Clinics serving an Indian population with an Indian board of directors can apply for federal Indian Health contracts.[34] California has greatly supplemented that effort,[35,36] and state funds can be applied for separately.

Clinics may also apply for Maternal and Child Health (MCH) funds, which are federal dollars administered by the state.[37,38] Contracts support prenatal, postpartum and well-infant care of poor people (not eligible for Medi-Cal) and seek to improve the quality of care through strong educational and social support systems. Many clinics in our survey did not apply for MCH contracts because there were too few patients in these categories to justify the contract development time. A network of clinics can feasibly share a contract, however, as well as sharing the required specialized providers.

Sanctions against the reimbursement of NP's and PA's by public fee-for-service programs. Patients can pay out-of-pocket to anyone for anything. Cash charges for services given solely by NP's and PA's are legal. Most private insurance companies will reimburse the services of an NP or PA when billed under the name of the supervising physician.

Medi-Cal[39] required direct physician involvement until August 1, 1978. This was a major barrier to remote clinics, many of which served predominantly Medi-Cal patients. Since then Medi-Cal-approved NP's and PA's under physician supervision have been eligible to bill at the same rates as physicians for typical primary care services.[31] This was a vital decision for the survival of many clinics.

Medicare, likewise, precluded NP and PA reimbursement.[40] However, Congress passed the Rural Health Clinic Act in 1977.[30,41] This Act specifically authorizes reimbursement (under both Medicare and Medicaid) for "reasonable costs" of NP's and PA's stationed away from supervising physicians in federally certified rural clinics. Not all rural facilities meet eligibility criteria.

NP's or PA's can be reimbursed for contraception services if their clinic has a contract with the California Office of Family Planning. This office joins federal funds[42] with a much larger state contribution[43] to pay for services to financially eligible patients. It was the first program to reimburse NP's and PA's. At present 150 nonprofit clinics have contracts. Some eligible clinics do not receive contracts due to limited funds. Other clinics choose not to seek these funds because of the complicated records required, according to our survey.

The Child Health and Disability Prevention Program (CHDP) reimburses NP and PA services if the supervising physician is participating in the program. Begun in 1975, CHDP has been mainly federally financed and state administered. It has a goal of assuring that every child from birth to age 21 receive periodic health screening.[44,45] Due to funding limitations, however, CHDP concentrates its efforts on children of school-entry age of low-income families.

Legal Issues

Unclear or restrictive legal roles and definitions of NP's and PA's. The California Physician's Assistant Act and subsequent administrative regulations[26,27] are quite specific about the privileges and constraints of PA's, as well as their training and certification. All PA's must pass a national physician's assistant examination. They are controlled by the Board of Medical Quality Assurance, which also approves a specific physician supervisor. PA constraints are further defined locally by standardized procedures, protocols, and standing orders. Since 1975 PA's have been

able to work at clinics remote from their supervising physicians.

Nurse practitioners are under different laws than physician's assistants. While there is yet no state licensure or certification as a nurse practitioner, "holding out" legislation[46] authorized the Board of Nursing to state criteria under which a nurse could call himself or herself a nurse practitioner. The criteria specify education.[47] (An NP does not have to take a national NP examination, but certification by an approved school or equivalency is required.) A nurse, however, can carry out the same tasks without meeting those criteria by not calling himself or herself a practitioner. Such a nurse would not be eligible for Medi-Cal reimbursement.

Nurses derive their authority to assess and manage patient problems from the Nurse Practice Act[28] and subsequent regulations.[29] The Act acknowledges the overlap of medicine and nursing and states guidelines for standardized procedures or protocols. Standardized procedures are written and signed by a nurse and his or her supervising physician, and authorize the nurse to take specific responsibilities in patient assessment. Management responsibility is shared. This law states no exclusions to potential privileges. The regulations allow, but do not require, written criteria for diagnosis and treatment of specific conditions.

Nurses who graduate from most primary care physician's assistant schools are eligible to become either NP's or PA's, or both.

Under these laws, the decision-making prerogatives of NP's and PA's are quite broad. At the individual facility the NP or PA and supervising physician decide together in what medical areas and to what level of responsibility the NP or PA should practice, given his or her training and experience. These decisions are then put in writing.

Legal sanctions against NP's and PA's prescribing drugs. An NP or PA cannot legally prescribe drugs in California.[48] The NP or PA may consult with a physician concerning each patient (including, by phone) and may then verbally transmit the physician's prescription to a pharmacist (except class II-controlled substances, mostly narcotics). Oddly, a nonphysician may not transmit an order in writing, although writing might reduce errors.

Case-by-case consultation is extremely inefficient and expensive, and may greatly hamper a remote clinic. "Transmittal of a physician's orders" has been interpreted to include standing orders or protocols, but this is by no means clear under the law.

Under demonstration legislation, beginning in mid-1979, a very few NP's, PA's and pharmacists are being allowed to prescribe from a limited formulary under the auspices of certain training projects.[49,50] Not all satellite NP's and PA's are eligible for this program, however, as not all are affiliated with the eight participating NP or PA projects.

Sanctions against NP's and PA's dispensing drugs. Dispensing drugs is limited to physicians and pharmacists under California law. This is a problem for remote clinics where there are no pharmacists. As with prescribing, demonstration legislation has authorized a limited number of projects to sponsor monitored dispensing of drugs by selected trainees.[49,50] The drug list is approved by both the supervising physician and the project. The NP or PA may use written standardized procedures or protocols as authorization to dispense a particular drug to a particular patient, and does not need specific physician approval for each instance. Again, as with the pilot prescribing program, not all remote NP's and PA's are affiliated with the approved projects. This remains a serious problem at some sites.

Summary and Discussion

Many health care problems have been faced by clinics trying to serve rural Californians by employing NP's or PA's (sometimes at distances from their supervising physicians).

Need is variously defined, and many groups including the poor, Chicanos and Indians, have special needs. NP's and PA's are increasing in number and availability, and some training programs and their funding sources have focused their attention towards rural or manpower shortage areas.

Physician supervision is defined by law and by required local guidelines, and it has been proved that the team concept can survive despite geographic separation. Support services, often a problem in rural areas, need be no more so for NP/PA clinics. Malpractice coverage and other forms of insurance are also available to most of these clinics.

Tax-supported programs have increased in number and are available to help establish and sustain clinics. These programs are diverse in their purposes, requirements and limitations.

The state of California has greatly increased direct tax support to rural clinics since 1976, supplementing more limited federal rural health funds. The state has also significantly supplemented federal Indian and Family Planning money, vital to many of these clinics.

The public programs of Medicare, Medi-Cal (Medicaid), Family Planning and Child Health and Disability Prevention now can reimburse NP's and PA's in many rural facilities. Medicare and Medi-Cal began reimbursement only in late 1978; this has been the most critical step for the survival of these clinics.

The current subsidies for rural clinics, at an all-time high, are probably temporary. County support, never very great, is even more restricted since the property tax initiative (Propositon 13, 1978). The state, however, had already assumed more responsibility for health care. Taxpayers, burdened by inflation, will probably vote to reduce this state funding in the next few years, and federal programs will probably be reduced as well. Indian and migrant programs will probably survive better than others. Fee-for-service programs have likely reached their peak, and national health insurance programs probably will not effectively include primary care. Clearly, health care for the poor remains a problem.

Prepaid group practice and foundation models as well as health maintenance organizations have had little impact on rural areas because they tend to attract large groups of organized employees with health care fringe benefits.

A few clinics are achieving self-sufficiency through patient charges, including receipt of out-of-pocket cash from patients. Cash payment may be the ultimate test of acceptance of NP's and PA's by the public, for it will have made the choice to pay NP's and PA's rather than travel further to see physicians (often at the same price). Patient acceptance, cost and choice for different health problems should be more carefully studied.

Legal issues still hinder NP's and PA's. There is no agreement on what constitutes a valid "standardized procedure" or to what degree of exactness protocols should be written. This is particularly an issue when an NP or PA "transmits a physician's valid prescription" and the protocol or standing order may or may not be "valid." NP's and PA's cannot dispense or prescribe drugs. Pilot legislation has attempted to deal with this problem, but not all satellite NP's and PA's are eligible; also, these experimental programs have been very slow in being initiated. Paradoxically, the dispensing law, implemented in 1972, is in some ways less restrictive. There is no pharmacist safeguard and no state formulary (as the prescribing act has) and, often, vague standardized procedures are still operating. In our opinion, the state will have to develop a licensure system for NP and PA dispensing and prescribing that will specify more clearly the definition and constraints of protocols and standing orders.

A broad base of public, community, legislative, professional and agency support has enabled many positive changes to occur. This strong support for NP/PA clinics is one answer to a need—and this support has been effective. Twenty-six NP and PA clinics have begun in California and the need and the resources exist for many more to follow.

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High-Noise Work Environment and Vocal Cord Dysfunction

WHEN SPEECH IS USED in the presence of excessive noise, there is a normal need to produce a louder and more projected voice. Vocal intensity and strain are increased proportionally in order to communicate in the high-noise environment. The fact that vocal strain contributes to vocal dysfunction has been well documented. As an occupational hazard, it has been related to only a limited number of professions. The results of a study suggest that vocal cord dysfunction is a much more prevalent infirmity as an occupational hazard than had been previously reported. The preliminary study indicated that the incidence of vocal cord dysfunction in an industrial population is roughly 8 percent. Taking into account the total number of persons employed in industry in this country, this suggests a potentially large pool of persons who are debilitated because of speaking in a noisy environment. . . . Of the vocal cord dysfunctions in this study, the most common cause noted was vocal cord nodules. Next in order were vocal cord polyps and chronic laryngitis. It is important to point out that high-noise work environment alone is not the only factor of concern in the development of vocal cord dysfunction. Cigarette smoking, excessive fumes, dust, metal filings and even work-related stress can contribute to vocal abuse. Use of the voice in a loud, abusive manner, however, is considered to be the major contributor to the development of vocal cord dysfunction in the work place.

—EUGENE RONTAL, MD, *Ann Arbor, Michigan*

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Precautions: Use with caution in individuals with histories of significant allergies and/or asthma. Do not rely on oral administration in patients with severe illness, nausea, vomiting, gastric dilatation, cardiospasm, or intestinal hypermotility. Occasional patients will not absorb therapeutic amounts given orally. In streptococcal infections, treat until the organism is eliminated (minimum of ten days). With prolonged use, nonsusceptible organisms, including fungi, may overgrow; treat superinfection appropriately.

Adverse Reactions: Hypersensitivity, including fatal anaphylaxis. Nausea, vomiting, epigastric distress, diarrhea, and black, hairy tongue. Skin eruptions, urticaria, reactions resembling serum sickness (including chills, edema, arthralgia, prostration), laryngeal edema, fever, and eosinophilia. Infrequent hemolytic anemia, leukopenia, thrombocytopenia, neuropathy, and nephropathy, usually with high doses of parenteral penicillin. [102175]

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ANESTHESIOLOGY

March 30-April 5—**Obstetric Anesthesia.** Ohio State University, Dept. of Anesthesiology, at Sheraton Waikiki Hotel, Oahu, Hawaii. One week. Contact: John S. McDonald, MD, Dept. of Anesthesiology, OSU, 410 W. 10th Ave., Columbus, OH 43210. (614) 422-5591.

CANCER

February 23—**Current Trends in Lung Cancer Diagnosis and Management—6th Annual Pulmonary Symposium.** USC and Inter-Community Hosp., Covina, at Calif. State Univ., Pomona. Saturday. 6 hrs. Contact: Linda Arbiter, MPH, Med. Ed. Coordinator, Inter-Community Hosp., 303 N. 3rd Ave., Covina 91723.

March 14—**Cancer of the Endometrium.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

March 15-16—**Pharmaceutical Aspects of Cancer Care—15th Annual San Francisco Cancer Symposium.** West Coast Cancer Foundation and American Cancer Soc. at Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: West Coast Cancer Foundation, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

EMERGENCY MEDICINE

March 9-15—**Mammoth Mountain Emergency Medicine Ski Conference.** UCI and Orange Co. Emergency Dept. Nurses' Assn. at Mammoth Lakes. Sunday-Saturday. 24 hrs. Cat. I CMA, ACEP; 24 elective credit hrs. AAFP. $250. Contact: Daniel Abbott, MD, Med. Conf., Inc., P.O. Box 52-B, Newport Beach 92662. (714) 642-7080.

March 17-21—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

April 12-13—**Symposium on Survival: An Analysis of Disaster Planning.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

April 12-19—**Emergency Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

April 17—**Infectious Disease for Emergency Physicians.** Goleta Valley Community Hospital and Assn. for Emergency Physicians for Ventura and Santa Barbara Counties at Goleta Valley Hosp., Santa Barbara. Thursday. 1½ hrs. CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

April 21-25—**Postgraduate Institute for Emergency Physicians,** Symposium I, UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

May 5-9—**Emergency Surgical Problems.** White Memorial Medical Center and LLU at Honolulu and Maui, Hawaii. Monday-Friday. 24 hrs. $200. Contact: Dir., Cont. Med. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000, ext. 1460.

May 11-17—**Modern Trends in Emergency Medicine.** Univ. of Hawaii, John A. Burns School of Medicine, Hawaii. One week. Contact: Delia M. Chang, CME, Univ. of Hawaii, John A. Burns Sch. of Medicine, 1960 East-West Rd., Honolulu 96822.

May 14—**Emergency Medicine Symposium.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

May 19-23—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 40 hrs. $300.

May 27-31—**American College of Emergency Physicians, California Chapter—1980 Scientific Assembly.** ACEP, Calif. Chap., and UCSD at Hotel del Coronado, Coronado. Tuesday-Saturday. Contact: UCSD.

June 10-13—**Radiology in the Emergency Room Department.** UCSF at Fairmont Hotel. Tuesday-Friday.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

June 17—**Death in the Emergency Department.** St. John's Hospital and Assn. for Emergency Physicians for Ventura and Santa Barbara Counties at St. John's Hospital, Oxnard. Tuesday; 8:00 p.m. 1½ hrs CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

June 23-27—**Advanced Emergency Medicine.** STAN. Monday-Friday. 25 hrs. $290.

June 23-27—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

June 27-28—**Ophthalmology and ENT for Emergency Room Physicians.** PMC. Friday-Saturday. 12 hrs.

July 14-18—**Medical Management of EMS Systems.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs.

July 21-25—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

MEDICINE

February 16—**5th Annual Liver Conference, Cholestasis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. $105. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave, Long Beach 90801. (213) 595-3811.

February 16-17—**Practical Gastroenterology for Primary Care Physicians.** UCLA at Miramar-Sheraton, Santa Monica. Saturday-Sunday. 12 hrs. $160.

February 16-23—**Clinical Allergy.** Univ. of Hawaii, John A. Burns Sch. of Med. at Maui Surf Hotel, Maui, Hawaii. One week. 28 hrs. $250. Contact: Delia M. Chang, Cont. Med. Ed., Univ. of HI, John A. Burns Sch. of Med., 1960 East-West Rd., Honolulu 96822.

February 21-24—**Federation of Western Societies of Neurological Science—Annual Meeting.** Biltmore Hotel, Santa Barbara. Thursday-Sunday. Contact: J. Carroll Ramseyer, MD, EEG/EMG Laboratory, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017.

February 22-23—**Medical Knowledge Self Assessment II.** American College of Physicians and PMC at Hyatt Regency, San Francisco. Friday-Saturday. 12 hrs. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

February 22-23—**Rehabilitation in Neurological Dysfunction.** PMC at Mark Hopkins Hotel, San Francisco. Friday-Saturday. 9 hrs. $135.

March 5—**Thyroid '80.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. Contact: Janie Sternal, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

March 7—**6th Annual Diabetes Program.** UCD at Red Lion Motor Inn, Sacramento. Friday. 6½ hrs.

March 7-9—**Northern California-Nevada Regional Meeting, American College of Physicians.** Doubletree Inn, Monterey. Friday-Sunday. Contact: Ralph O. Wallerstein, MD, 3838 California St., San Francisco 94118.

March 10-12—**The Major Lung Diseases 1980: An Integrated Pathologic-Clinical Review.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 18 hrs. $250.

March 11-13—**Pulmonary Complications of Trauma.** Alta Bates Hospital, Calif. Society for Respiratory Therapy, American Lung Assn. of Alameda Co. at Hyatt Lake Tahoe, Incline Village. Tuesday-Thursday. 9 hrs. Contact: Claudia F. Read, Medical Ed., Alta Bates Hosp., 3001 Colby, Berkeley 94705. (415) 845-7110, ext. 2031.

March 13-16—**Pediatric Cardiology—A Growing Concern: What the Primary Care Physician Should Know.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Sunday. 11 hrs.

March 16-19—**Basic Cardiology for the Primary Care Physician.** UCSF at Yosemite. Sunday-Wednesday.

March 21-23—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Jack Tar Hotel, San Francisco. Friday-Sunday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

March 24-26—**4th Annual Review and Update of the Immunology and Clinical Practice of Allergy.** USCD at Hilton, San Diego. Monday-Wednesday. 20 hrs. $225.

March 24-April 4—**Intensive Review of Internal Medicine.** USC. Two weeks.

March 26-28—**Endocrine Glands in Health and Disease.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday.

March 27-29—**Scientific Basis of Respiratory Care: Present State-of-the-Art and Future Directions.** American College of Chest Physicians at Sheraton-Palace, San Francisco. Thursday-Saturday. 16 hrs. $165, ACCP members; $185, nonmembers. Contact: Dale E. Braddy, Dir. of Ed., ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200.

March 29-April 5—**Infectious Diseases.** Univ. of Washington School of Medicine at Naniloa and Kona Surf Hotels, Hilo, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 7-16—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 9—**Cardiovascular Disease.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Memorial Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

April 9—**Asthma in Childhood.** See Pediatrics, April 9.

April 9-June 11—**Practical Dermatology for the Practicing Internist.** UCLA. 10 Wednesday evenings. 20 hrs.

April 10-11—**Advances in Infectious Diseases: Prophylactic Antibiotics in Medicine and Surgery.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday. 14 hrs. $150.

April 10-13—**Current Concepts and Advances in Diagnosis, Management and Prevention of Cardiac and Cardiopulmonary Diseases.** American Medical Assn. and American College of Cardiology at Los Angeles. Contact: AMA, 535 N. Dearborn, Chicago 60610. (312) 751-6000.

April 11—**Bronchial Asthma.** UCD at Hyatt on Union Square, San Francisco. Friday.

April 12-19—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

April 25-27—**New Concepts in Clinical Electrocardiography.** American College of Cardiology at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 26-27—**Practical Rheumatology.** UCLA. Saturday-Sunday.

April 28-30—**Pediatric Dermatology.** STAN at Rancho Mirage. Monday-Wednesday. 18 hrs. $195.

April 30—**Office Management of Hypertension.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Wednesday. 4 hrs.

May 2-4—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Sunday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

May 2-4—**Headache Management: Therapeutic Workshops.** UCLA at Newporter Inn, Newport Beach. Friday-Sunday.

May 3—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

May 9-11—**The Many Faces of Headache.** UCD at Holiday Inn, Napa Valley. Friday-Sunday.

May 10—**Cardiology Conference.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

May 15-17—**Acute Myocardial Infarction.** PMC at St. Francis Hotel, San Francisco. Thursday-Saturday. 15 hrs.

May 16-18—**Cardiac Rehabilitation.** International Medical Education Corp. at Jack Tar Hotel, San Francisco. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

May 19-24—**4th Bi-Annual Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday.

May 30—**Team Approach to Arthritis.** PMC and Arthritis Foundation. Friday. 6 hrs. $85.

May 31-June 1—**Pediatric Dermatology.** UCLA. Saturday-Sunday.

June 2-6—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday. 34 hrs.

June 9-13—**Advances in Internal Medicine.** UCSF. Monday-Friday. 34 hrs.

June 11-14—**7th Annual Symposium on Clinical Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Wednesday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 20-21—**Medical Knowledge Self Assessment—Group C.** American College of Physicians and PMC at Hyatt Regency, San Francisco. Friday-Saturday. Contact: PMC.

June 27-29—**Hepatobiliary Disease in Clinical Practice.** American College of Physicians at Holiday Inn on Union Square, San Francisco. Friday-Sunday. 15 hrs. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

July 8-10—**Podiatric Dermatology.** STAN. Tuesday-Thursday. 17 hrs.

July 12-19—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 23 hrs. $290.

OBSTETRICS AND GYNECOLOGY

March 12—**Vaginitis.** LLU. Wednesday. 4 hrs.

March 14-15—**25th Annual Postgraduate Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Shirley Gach, SCPMG, Education and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4242.

March 22-23—**Contraception: Current Research and Multidisciplinary Applications.** See Of Interest To All, March 22-23.

May 12-14—**Recent Advances in Ob/Gyn.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

May 16-18—**Ob/Gyn.** UCLA at Ojai Valley Inn, Ojai. Friday-Sunday. 12 hrs. $300.

June 5-7—**Gynecologic Urology: Theory and Practice, Basic and Advanced.** Mem. Hosp. Med. Ctr.-UCI Ctr. for Health Education at Inn at the Park, Anaheim. Thursday-Saturday. 20 hrs. $300. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

PEDIATRICS

February 21-23—**Practical Orthopedics for the Pediatrician.** Children's Hospital Medical Center of Northern Calif. at Sahara Tahoe Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, Med. Staff Office, Children's Hosp. Med. Ctr., 51st and Grove Sts., Oakland 94609. (415) 654-5600, ext. 215.

February 23—**Pediatric Review.** UCLA. Saturday.

March 5-7—**Pediatric Pulmonary Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 8—**Adolescent Medicine.** UCLA. Saturday.

March 13-16—**Pediatric Cardiology.** See Medicine, March 13-16.

April 4-5—**Pediatric Topics 1980.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 9 hrs. $80.

April 9—**Asthma in Childhood.** LLU. Wednesday. 4 hrs. $30.

April 11-12—**Pediatric Symposium—22nd Annual.** So. Calif. Permanente Medical Group at Sheraton Hotel, Anaheim. Friday-Saturday. Contact: Shirley Gach, Ed. and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

April 26-27—**The Special Child.** See Psychiatry, April 26-27.

April 28-30—**Pediatric Dermatology.** See Medicine, April 28-30.

May 3—**Pediatric Dermatology Seminar.** See Medicine, May 3.

May 5-9—**Pediatric Review—10th Annual.** USC. Monday-Friday.

May 7-9—**Care of the Sick Newborn.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 18 hrs. $130. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 8-10—**Annual Pediatrics Course.** UCSF. Thursday-Saturday.

May 21-25—**Pediatrics for the Primary Care Physician.** UCD at Red Lion Motor Inn, Sacramento. Wednesday-Sunday. 18 hrs.

May 31-June 1—**Pediatric Dermatology.** See Medicine, May 31-June 1.

June 14-21—**Pediatric Workshop.** USC at Royal Lahaina, Maui, Hawaii. One week. 22 hrs. $325.

PSYCHIATRY

March 15—**The Void—Treatment of a Narcissistic Patient.** No. Calif. Psychiatric Society and McAuley Institute at St. Mary's Hospital, San Francisco. Saturday. 3 hrs. $15. Contact: George L. Ponomareff, MD, 2457 Grove Way, Suite 102, Hayward 94546.

March 21-23—**Narcissism—A Multidimensional View.** UCSF. Friday-Sunday.

April 10-May 15—**Films and Psychiatry.** PMC. Thursday evenings. 18 hrs. $75.

April 26-27—**The Special Child.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

May 5-9—**American Psychiatric Association.** Hilton, San Francisco. Monday-Friday. Contact: APA, 1700 18th St. NW, Washington, DC 20009.

June 22-27—**Comparative Psychotherapies.** USC at Hilton, San Diego. Monday-Friday.

RADIOLOGY AND PATHOLOGY

February 22—**Practical Laboratory Mycobacteriology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 27-29—**Sierra Radiology Conference—Radiology of Problems in Clinical Medicine.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at Sahara Tahoe Hotel, South Lake Tahoe. Wednesday-Friday. 18 hrs. $215. Contact: Michael H. Reid, PhD, MD, Prog. Dir., Sacramento Radiology Research and Education Foundation, P.O. Box 161112, Sacramento 95816.

March 1-2—**Concepts and Controversies in Cardiopulmonary Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 11 hrs. $150.

March 3-7—**Diagnostic Radiology.** UCSF. Monday-Friday.

March 8-9—**A Practical Course in B-Scan Ultrasound.** UCSF. Saturday-Sunday.

March 10-12—**The Major Lung Diseases 1980: An Integrated Pathologic-Clinical Review.** See Medicine, March 10-12.

March 13—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 24-28—**Abdominal Radiology Update 1980.** UCSD at Vacation Village, San Diego. Monday-Friday. 36 hrs.

April 10—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 13-18—**American Association of Pathologists.** Anaheim. Sunday-Friday. Contact: AAP, 9650 Rockville Pike, Bethesda, MD 20014.

May 17—**Recent Advances in Pathology.** UCSF at Hyatt on Union Square, San Francisco. Saturday. 8 hrs. $90.

June 10-13—**Radiology in the Emergency Room Department.** See Emergency Medicine, June 10-13.

June 16-25—**Radiology of Bone and Joint Disease.** UCSD at Hotel del Coronado, Coronado (June 16-19) and Kauai Surf Resort Hotel, Kauai, Hawaii (June 23-25). 7 days. 29 hrs. $500 (or $300 for first part; $200, second part).

June 22-27—**Pathology of the Lung.** UCSD. One week. 50 hrs. $450.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

March 1—**Corneal-External Ocular Disease Surgery Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

March 1-8—**Western Section American Urological Association —Annual Meeting.** Kona/Honolulu, Hawaii. One week. Contact: Western Section AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

March 7-8—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

March 15-19—**Controversial Areas in Surgery—17th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 19-23—**Vascular Surgery—8th Annual Symposium.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 25-29—**3rd U.S. Intraocular Lens Symposium and 7th Scientific Session.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Tuesday-Saturday. 30 hrs. Contact: Debbi Miller, Dir. of Mtg. Services, AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 395-3937.

April 3-4—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 10-11—**Advances in Infectious Diseases: Prophylactic Applications in Medicine and Surgery.** See Medicine, April 10-11.

April 18-19—**Workshop on Orthopedic Injuries.** PMC. Friday-Saturday.

April 19-20—**Office Orthopedics/Office Urology.** UCLA. Saturday-Sunday.

April 24-25—**11th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. Contact: Mrs. Lu Hendricks, JSEI, UCLA Sch. of Med., Los Angeles 90024.

April 24-26—**General Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday.

April 26-May 3—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

April 28-30—**American Association for Thoracic Surgery.** Hilton Hotel, San Francisco. Monday-Wednesday. Contact: AATS, 6 Beacon St., Suite 620, Boston, MA 02108.

May 4—**Recent Advances in Surgery of the Lower Gastrointestinal Tract.** White Memorial Medical Center and LLU at Bonaventure Hotel, Los Angeles. Sunday. 8½ hrs. Contact: Dir., Cont. Med. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000.

May 5-6—**Neurosurgical Contributions to Daily Medical Practice.** UCSD at Vacation Village, San Diego. Monday-Tuesday. 16 hrs. $160.

May 9-10—**Combined Otolaryngologic/Orthognathic Symposium.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Friday-Saturday. 12 hrs. $195.

May 10—**Photocoagulation Therapy Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

May 15-17—**Nasal Plastic and Reconstructive Surgery.** PMC at Clift Hotel, San Francisco. Thursday-Saturday. 15 hrs. $250.

May 18-22—**American Urological Association.** Hilton, San Francisco. Sunday-Thursday. Contact: AUA, 1120 N. Charles St., Baltimore, MD 21201.

May 29-31—**Oto '80.** Project HEAR at St. Francis Hotel, San Francisco. Thursday-Saturday. 24 hrs. $485. Contact: Judy Staton Thielke, Project HEAR, 1801 Page Mill Rd., Palo Alto 94304. (415) 494-2000.

June 3-6—**25th Annual Samuel Higby Camp Lectureship and 15th Annual Scientific Program of the LeRoy C. Abbott Orthopaedic Society.** UCSF. Tuesday-Friday. 14 hrs. Contact: Mark Parsons, Alumni Sec., UCSF, Room U471, San Francisco 94143. (415) 666-1166.

June 5-6—**Neurosurgery Postgraduate Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Friday. 17 hrs. $225.

June 6-7—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

June 7—**Glaucoma Surgery Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

June 7-13—**Orthopedic Review Course.** UCSF at Hyatt on Union Square, San Franciso. One week. 50 hrs.

June 8-14—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

June 11—**Problems in Postoperative Management and the Surgical Intensive Care Unit.** LLU. Wednesday. 4 hrs. $30.

June 14-21—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $325.

June 19-20—**Office Orthopedics.** USC. Thursday-Friday.

June 19-21—**Highlights of Ophthalmology.** PMC at Hyatt Regency, San Francisco. Thursday-Saturday. $225.

July 12-19—**Cardiovascular Medicine and Surgery: An Advanced Course.** See Medicine, July 12-19.

OF INTEREST TO ALL PHYSICIANS

February 15-16—**Health Care and the Changing Society.** Vista Hill Foundation and Mesa Vista Hosp. at Hotel del Coronado, Coronado. Friday-Saturday. 9 hrs. Contact: Virginia Everett, Vista Hill Foundation, 3420 Camino del Rio, Suite 100, San Diego 92108. (714) 563-1770.

February 21-22—**New and Old Antibiotics.** USC. Thursday-Friday.

February 21-23—**Musculoskeletal Diagnostics and Treatment—Towards a More Rational Perspective.** American Academy of Physical Medicine and Rehabilitation and Eisenhower Med. Ctr. at Gene Autry Hotel, Palm Springs. Thursday-Saturday. Contact: Paul H. Goodley, MD, Pain Diagnostics and Rehabilitation Institute, 2210 W. 3rd St., Los Angeles 90057. (213) 383-8485.

February 22-23—**Rehabilitation in Neurological Dysfunction.** See Medicine, February 22-23.

February 23-24—**Health in the Workplace.** UCSF Cont. Ed. Health Sciences. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

February 24-26—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Sunday-Tuesday. 21 hrs. $250.

February 25-29—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $290.

February 26-March 2—**Critical Care Medicine.** USC at Hilton, San Francisco. Tuesday-Sunday.

February 27—**Hospital Infection Control.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 7 hrs. Contact: Prog. Coord., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 27—**Drug Update—1980—18th Annual Symposium.** Eden Hospital, Castro Valley. Wednesday. Contact: Jay J. Protass, MD, Eden Hospital, 20103 Lake Chabot Rd., Castro Valley 94546. (415) 537-1235.

March 1—**New Frontiers in Clinical Medicine.** PMC. Saturday. 6 hrs. $85.

March 1-2—**Genetic Disorders.** UCLA. Saturday-Sunday.

March 1-2—**Health Communication for Providers and Consumers.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday. 11 hrs. Contact: UCSF Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

March 1-2, 15-16—**Basic and Advanced Hypnosis.** San Francisco Academy of Hypnosis at Children's Hospital, San Francisco. Two weekends. 28 hrs. $270. Contact: Jan Brooks, SF Academy of Hypnosis, 2820 15th Ave., San Francisco 94127.

March 3-5—**Orthopedics for the Primary Physician.** Bone and Joint Disease Foundation, San Diego. Monday-Wednesday. Contact: Bone and Joint Disease Fndn., P.O. Box 82441, San Diego 92138. (714) 294-5944.

March 5, 12, 19, April 2, 9, 16—**General Preventive Medicine.** USC. Wednesday evenings.

March 8-9—**Approaches to Healing—3rd Annual Course.** San Diego County Medical Society and UCSD at Town and Country Hotel, San Diego. Saturday-Sunday. 12 hrs. $150. Contact: Roger L. Youmans, MD, SDCMS, P.O. Box 23015, San Diego 92123.

March 8-9—**Clinical Hypnosis: Advanced Seminar.** San Diego and American Societies for Clinical Hypnosis, Education Research Fndn., Bay General Community Hosp. at Admiral Kidd Club, San Diego. Saturday-Sunday. 14 hrs. Contact: Errol R. Korn, MD, 480 4th Ave., Suite 409, Chula Vista 92010. (714) 420-8051.

March 9-15—**Critical Care II and Ski.** College of Medical Education, Pierce Co. (WA) Med. Soc. at Sahara Lake Tahoe, Incline Village. One week. Contact: Maxine Bailey, College of Med. Ed., Pierce Co. Med. Soc., 705 S. 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 9-16—**Sports Medicine.** Center for Sports Medicine, Northwestern Univ. Med. Sch.; Div. of Sports Med., No. Carolina Dept. of Public Instruction at Intercontinental Hotel, Maui, Hawaii. One week. Contact: Marianne Porter, Ctr. for Sports Med., 2-063, 303 E. Chicago Ave., Chicago 60611.

March 12—**Refresher in Family Practice.** N. T. Enloe Memorial Hosp. at Holiday Inn, Chico. Wednesday. 6 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 283.

March 15—**Medical Treatment of Alcoholism.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7 hrs.

March 15-16—**Practical ENT for Primary Care Physicians.** UCLA. Saturday-Sunday.

March 18-21—**Clinical Management.** STAN at The Lodge, Pebble Beach. Tuesday-Friday. 12 hrs. $150.

March 18-22—**Sports Medicine.** University of Hawaii School of Medicine at Princess Kaiulani Hotel, Waikiki, Honolulu, Hawaii. Tuesday-Saturday. 18 hrs. $200. Contact: Hawaii Conference Services, P.O. Box 25055, Honolulu 96825. (808) 377-6445.

March 19-21—**American Society for Clinical Pharmacology and Therapeutics.** Fairmont Hotel, San Francisco. Wednesday-Friday. Contact: E. H. Funk, Jr., MD, ASCPT, 1718 Gallagher Rd., Norristown, PA 19401.

March 22—**Otolaryngology for the Primary Care Physician.** Institute for Medical Education and Research, San Diego. Saturday. Contact: Inst. for Med. Ed. and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126.

March 22-23—**Contraception: Current Research and Multidisciplinary Applications.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

March 24-28—**Postgraduate Institute for Primary Care Physicians.** UCSD at Vacation Village, San Diego. Monday-Friday.

March 31-April 2—**Football Injury Workshop.** Center for Sports Medicine, St. Francis Memorial Hospital at Jack Tar Hotel, San Francisco. Monday-Wednesday. $165. Contact: Ctr. for Sports Medicine, St. Francis Mem. Hosp., 900 Hyde St., San Francisco 94109. (415) 775-4321, ext. 3370.

April 6-9—**Clinical Dermatology for the Family Practitioner.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Wednesday. 14½ hrs. $125.

April 8, 15, 22, 29, May 3—**Therapeutic Movement, Manipulation and Massage.** UCLA. Tuesdays.

April 9-12—**Nosocomial Infection.** Memorial Hospital Medical Center-UCI Center for Health Education. Wednesday-Saturday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 12—**Medical Applications of Exercise for the Primary Care Physician.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 9 hrs.

April 17-19—**Wound Management Workshop.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

April 21-25—**1980 Family Practice Review.** PMC at Hilton Hotel, Oakland Airport. Monday-Friday. 27 hrs. $350.

April 24-27—**Postgraduate Institute.** CMA and USC at Ahwahnee Hotel, Yosemite. Thursday-Sunday. Contact: Charlotte Newhart, CMA.

May 1-2—**Therapeutic Drug Monitoring.** PMC. Thursday-Friday. 12 hrs.

May 1-4—**4th Annual Basic Clinic Hypnosis Workshop.** UCI at Balboa Bay Club, Newport Beach. Thursday-Sunday. 30 hrs. $310.

May 2-3—**Providence Hospital Annual Spring Seminar.** Claremont Hotel, Oakland. Friday-Saturday. Contact: Medical Staff Office, Providence Hosp., 3100 Summit St., Oakland 94623. (415) 835-4500, ext. 2032.

May 3-4—**Holistic Medicine: The Pursuit of Wellness.** UCSF and State Dept. of Health Services at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: UCSF Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

May 10, 24—**Clinical Nutrition.** UCLA. Two Saturdays.

May 12-15—**Aerospace Medical Association.** Disneyland Hotel, Anaheim. Monday-Thursday. Contact: R. R. Hessberg, MD, Washington Nat'l Airport, Washington, DC 20001.

May 13-19—**Basic Diving Medicine.** UCSF at Fresno. One week.

May 14—**Deafness and Its Management.** LLU. Wednesday. 4 hrs. $30.

May 16-18—**2nd Annual National Symposium on Sexuality and Disability.** UCSF at Claremont Hotel, Berkeley. Friday-Sunday. Contact: UCSF Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

May 17-18—**Advanced Therapeutics in Clinical Nutrition.** St. Francis Memorial Hospital and American Society of Parenteral and Enteral Nutrition at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: Elena Tinloy, PharmD, St. Francis Mem. Hosp., P.O. Box 7726, San Francisco 94120. (415) 775-4321, ext. 3323.

May 18-23—**Fingers-to-the-Toes: An Orthopaedic Approach for the Family Practitioner.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Friday.

May 19-23—**7th Annual Family Practice Refresher Course.** UCLA and Santa Monica Hospital Medical Center at Sheraton-Miramar, Santa Monica. Monday-Friday. Contact: UCLA.

June 7-8—**Nutrition: Myths and Realities.** UCSF and Institute for the Study of Human Knowledge at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

June 11-13—**Clinical Application of Hyperbaric Oxygen—5th Annual Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 24 hrs. Contact: G. B. Hart, MD, Dir., Baromedical Dept., Mem. Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801.

June 16-21—**Family Practice Refresher Course—11th Annual.** UCI at Marriott Inn, Newport Beach. Saturday-Thursday. 49 hrs. $335.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

March 20—**Treatment Outcome Study, Harborview Community Health Center—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

March 26—**Utilization of Midlevel Practitioners—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

May 1—**Child and Community Psychiatry—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

May 28—**Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday, 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

June 19—**Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

MONTANA

February 20-22—**Diagnosis and Management of Bleeding Disorders—Univ. of Wash. Internal Medicine Review Sessions.**

February 20, Wednesday, Great Falls, 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 21, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

February 22, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

February 23-24—**Annual Mid-Winter Meeting, Montana Academy of Dermatology.** Big Sky. Saturday-Sunday. Huntley Lodge. Contact: John R. Tkach, MD, 300 N. Willson, Bozeman, MT 59715. (406) 587-5442.

February 29-March 1—**Annual Medical Seminar.** Big Sky. Friday-Saturday. Huntley Lodge. Contact: D. Frank Johnson, MD, Interhospital Continuing Medical Education Department, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 12—**Pediatric Hematology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 26-28—**The Eye and Internal Disease—Univ. of Wash. Internal Medicine Review Sessions.**

March 26, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 27, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

March 28, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 9—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 16-18—**Office Gynecology—Univ. of Wash. Internal Medicine Review Sessions.**

April 16, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 17, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

April 18, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 18-19—**Montana Medical Association's 1980 Interim Meeting.** Helena. Friday-Saturday. Contact: G. Brian Zins, Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

May 7—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28-30—**Nuclear Medicine for Internists—Univ. of Wash. Internal Medicine Review Sessions.**

May 28, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 29, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

May 30, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 52 West Pine, Missoula, MT 59801. (406) 549-3782.

June 11-13—**Transient Ischemic Attack and Stroke; Seizure Disorders—Univ. of Wash. Internal Medicine Review Sessions.**

June 11, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

June 12, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

June 13, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

IDAHO

February 23-March 1—**Office Orthopedics for Primary Physicians.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 26—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

March 1-8—**Current Concepts in Medicine—Good Samaritan Hospital, San Jose, California.** Sun Valley. Saturday-Saturday. Contact: Daman-Nelson Travel, 115 Mission St., San Francisco, CA 94105. (415) 982-3307.

March 8-15—**Psychiatry for Primary Physicians.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 15-22—**Sports Medicine.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 17—**Shock in Pregnancy—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

March 25—**Pediatric Arthritis and Immunology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

April 14—**Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

April 22—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

May 19—**Hypertension and Pregnancy—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 20—**Dysmorphology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony's Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

OF INTEREST TO ALL PHYSICIANS

June 17-20—**American College of Physicians Review Course.** Portland, Tuesday-Friday. Jantzen Beach Thunderbird. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 25-27—**Symposium on Sports Medicine.** Eugene, Wednesday-Friday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

February 15—**Peripheral Vascular Disease.** Tacoma. Friday. Tacoma General Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

February 18—**Endocrinology Circuit Course.** Vancouver, WA. Monday (4 hours). St. Joseph Community Hospital. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 19—**Endocrinology Circuit Course.** Longview. Tuesday (4 hours). Monticello Medical Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 20—**Endocrinology Circuit Course.** Olympia. Wednesday (4 hours). Tyee Motor Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 21—**Endocrinology Circuit Course.** Bremerton. Thursday. Harrison Memorial Hospital. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 22—**Endocrinology Circuit Course.** Bellingham. Friday. Western Washington University. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 22-23—**Psychiatric Management of the Problem of Pain.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

February 23-March 1—**Office Orthopedics for Primary Physicians.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 25—**Renal Pathophysiology and Renal Failure—Univ. of Wash., Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

February 26—**Gyn Oncology—Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

February 28-29—**Northwest Stroke Symposium.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: Education and Training Department, Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

March 6-7—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 7—**Birth Control—State of the Art, 1980.** Seattle. Friday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital, 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

March 8-15—**Psychiatry for Primary Physicians.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 9-15—**Critical Care II and Ski.** Lake Tahoe, Nevada. Thursday-Wednesday. Sahara Tahoe. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 11—**Pediatric Hematology—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m. Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medicine Center, Spokane, WA 99204. (509) 455-8220.

March 13-14—**Tacoma Academy of Internal Medicine Annual Scientific Program.** Tacoma. Thursday-Friday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 14-15—**Pharmacology for the Practitioner.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

March 15-22—**Sports Medicine.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 17-28—**Rehabilitation Medicine Review.** Seattle. Two weeks. University Towers Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 18—**Shock in Pregnancy—Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

March 21-22—**Days of Pediatrics.** Tacoma. Friday-Saturday. Mary Bridge Children's Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98450. (206) 627-7137.

March 24—**Ischemic Heart Disease—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 24-28—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 29-April 5—**Infectious Diseases.** Hilo, Hawaii. Saturday-Saturday. Naniloa and Kona Surf Hotels. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 31-April 3—**American College of Physicians: Hematology.** Seattle. Monday-Thursday. Olympic Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 3-4—**Hazards to the Fetus.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 8—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

April 10-11—**Dermatology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 10-11—**Annual Cancer Symposium—Gastrointestinal.** Seattle. Thursday-Friday. Swedish Hospital and Medical Center. Contact: John L. Wright, MD, Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

April 12—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

April 15—**Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

April 17-18—**Couples.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 18-19—**Tacoma Surgical Society Annual Scientific Program.** Tacoma. Friday-Saturday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

April 24-25—**Respiratory Care.** Seattle. Thursday-Friday. Contract: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 24-25—**Review of Arrythmias.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 25-26—**Anesthesia: Low Flow States—Pathology and Treatment.** Vancouver. British Columbia. Friday-Saturday. Four Seasons Hotel. Contact: Dr. K. Turnbull, Academy of Medicine, 1807 West 10th Avenue, Vancouver, BC V6J 2A9.

April 28—**Cardiomyopathies and Pericardial Disease—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 1-2—**Controversies in Medicine.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 2-3—**Contemporary Clinical Neurology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 5-6—**Patient-Physician Relationship.** Port Ludlow. Monday-Tuesday. The Admiralty. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 6—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Spokane). 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

May 8-10—**Washington Academy of Family Physicians—Annual Scientific Assembly.** Seattle. Thursday-Saturday. Red Lion Inn/Seattle-Tacoma Airport. 14 prescribed hours. Contact: Carolyn M. Palmer, Washington Academy of Family Physicians, 3700 140th Ave., NE, Bellevue, WA 98005. (206) 883-8852.

May 12—**Principles of Antibiotic Therapy—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 16-17—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 20—**Hypertension and Pregnancy—Univ. of Wash. OB-GYN Sessions** (Spokane). 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 22-23—**Adolescent Medicine.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 30—**Ophthalmology in Family Practice.** Seattle. Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 6-7—**Workshops in Musculoskeletal Disease.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Renal Disease.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 19-20—**Laboratory Medicine.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 23—**Basic Concepts of Immunology and Their Application—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

June 26-27—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 28-July 5—**Alaska Cruise—Emergency Medical Care: Trauma, Orthopedics and Surgery; Biomedical History.** 8 days. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

July 25-26—**Seafair II Anesthesia Meeting**—Washington State Society of Anesthesiologists. Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Sandra McDonald, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

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February 15-19
SPONSOR: University of Utah
TITLE: **The Heart and Peripheral Vascular System—25th Annual Postgraduate Course in Anesthesiology**
LOCATION: Hotel Utah, Salt Lake City
FEE: $200
CREDIT: 16 hours
CONTACT: Theodore Stanley, MD (801) 581-6393

February 21-23
SPONSOR: University of Utah
TITLE: **21st Annual Obstetrics and Gynecology Course**
LOCATION: Holiday Inn, Park City, Utah
FEE: $250
CREDIT: 16.5 hours
CONTACT: David Engleberg (801) 581-3087

February 24-March 1
SPONSOR: University of Utah
TITLE: **Radiology of the Traumatized and Acutely Ill Patient**
LOCATION: Park City, Utah
FEE: $240
CREDIT: 20 hours
CONTACT: Rebecca Peay (801) 581-8118

February 25-27
SPONSOR: University of Utah
TITLE: **Practical Pediatrics Review and Update**
LOCATION: Salt Lake Hilton
FEE: $150
CREDIT: 16 hours
CONTACT: Dennis Ashton, MD (801) 942-1800

February 28-March 1
SPONSOR: Salt Lake Surgical Center
TITLE: **6th Annual Meeting—Society for the Advancement of Free Standing Ambulatory Surgical Care**
LOCATION: Hotel Utah, Salt Lake City
FEE: Members—$170
Non-members—$195
Nurses—$95
CREDIT: 16 hours
CONTACT: Harry Wong, MD (801) 261-3141

February 29
SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology**
LOCATION: 7th Floor Conf. Room, LDS Hospital, Salt Lake City
FEE: $25
CREDIT: 3 hours
CONTACT: Stanley Everett (801) 350-1867

March 7-8
SPONSOR: UAFP
TITLE: **UAFP Annual Meeting**
LOCATION: Little America, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Janet Davis (801) 466-9478

March 7-8
SPONSOR: University of Utah
TITLE: **Emergency Medical Service Seminar**
LOCATION: St. George Hilton, St. George
FEE: To be announced
CREDIT: To be announced
CONTACT: Warren Stucki, MD (801) 628-1641

March 8
SPONSOR: Hill Air Force Hospital
TITLE: **Emergency Procedures**
LOCATION: HAFB Hospital Phys. Exam. Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

March 12-14
SPONSOR: InterWest Regional Med. Ed. Center
VA Medical Center
TITLE: **Neurological Update for Physicians and Nurses**
FEE: To be announced
CREDIT: To be announced
CONTACT: Ida Bickle, RN (801) 582-1565 (Ext. 681)

March 14
SPONSOR: Hill Air Force Hospital
TITLE: **Common ER Surgical Procedures**
LOCATION: HAFB Hospital Phys. Exam. Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

March 17-21
SPONSOR: University of Utah
TITLE: **Advances in Internal Medicine Conference**
LOCATION: Snowbird, Utah
FEE: $200
CREDIT: 22.5 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

SPONSORS OF COURSES—ABBREVIATIONS

AF	Arthritis Foundation
HAFB	Hill Air Force Base
LDSH	LDS Hospital
MDH	McKay-Dee Hospital
OEH	Center/Occupational & Environmental Health
PCMC	Primary Children's Medical Center
SLSC	Salt Lake Surgical Center
UAFP	Utah Academy of Family Practice
UU	University of Utah
UVH	Utah Valley Hospital
VAH	Veteran's Administration Hospital
SHCC	Shriners Hospital for Crippled Children

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-9, 1980, McKinley Village Lodge.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 23-27, 1980, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: February 8-13, 1980, Town and Country, San Diego.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 24-27, 1980, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: 1980—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1980, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 2-4, 1980, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 16-18, 1980, MGM Grand, Las Vegas.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 7-9, 1980, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-31, 1980, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 30-October 3, 1980, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 2-5, 1980, Thunderbird at Jantzen Beach, Vancouver, WA.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 23-27, 1980, Snow King Inn, Jackson.

March 21

SPONSOR: Shriners Hospital for Crippled Children
TITLE: **18th Annual Scientific Session**
LOCATION: Shriners Hospital, Salt Lake City
FEE: To be announced
CREDIT: 12 hours
CONTACT: Grace Miya (801) 532-5307

March 21

SPONSOR: Hill Air Force Hospital
TITLE: **Emergency Transportation Problems and Abdominal Trauma**
LOCATION: HAFB Hospital Phys. Exam. Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

March 24-28

SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird, Utah
FEE: $200
CREDIT: 22.5 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

March 27-29

SPONSOR: Rocky Mountain Center for Occupational and Environmental Health/Harvard School of Public Health
TITLE: **2nd Annual Park City Environmental Health Conference**
LOCATION: Park City, Utah
FEE: Pending
CREDIT: 20 hours
CONTACT: Katharine Blosch (801) 581-7182

March 29

SPONSOR: Utah Heart Association
TITLE: **Scientific Session**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Florence Christensen (801) 322-5601

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

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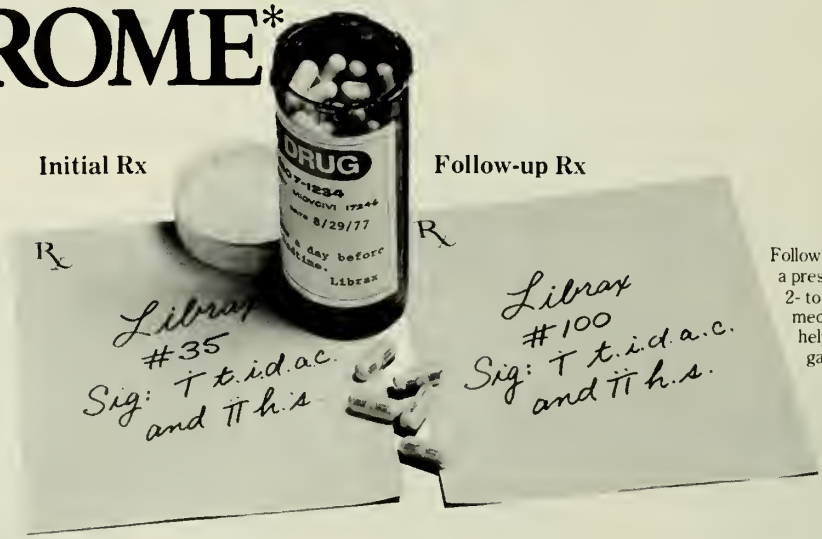

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"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

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As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

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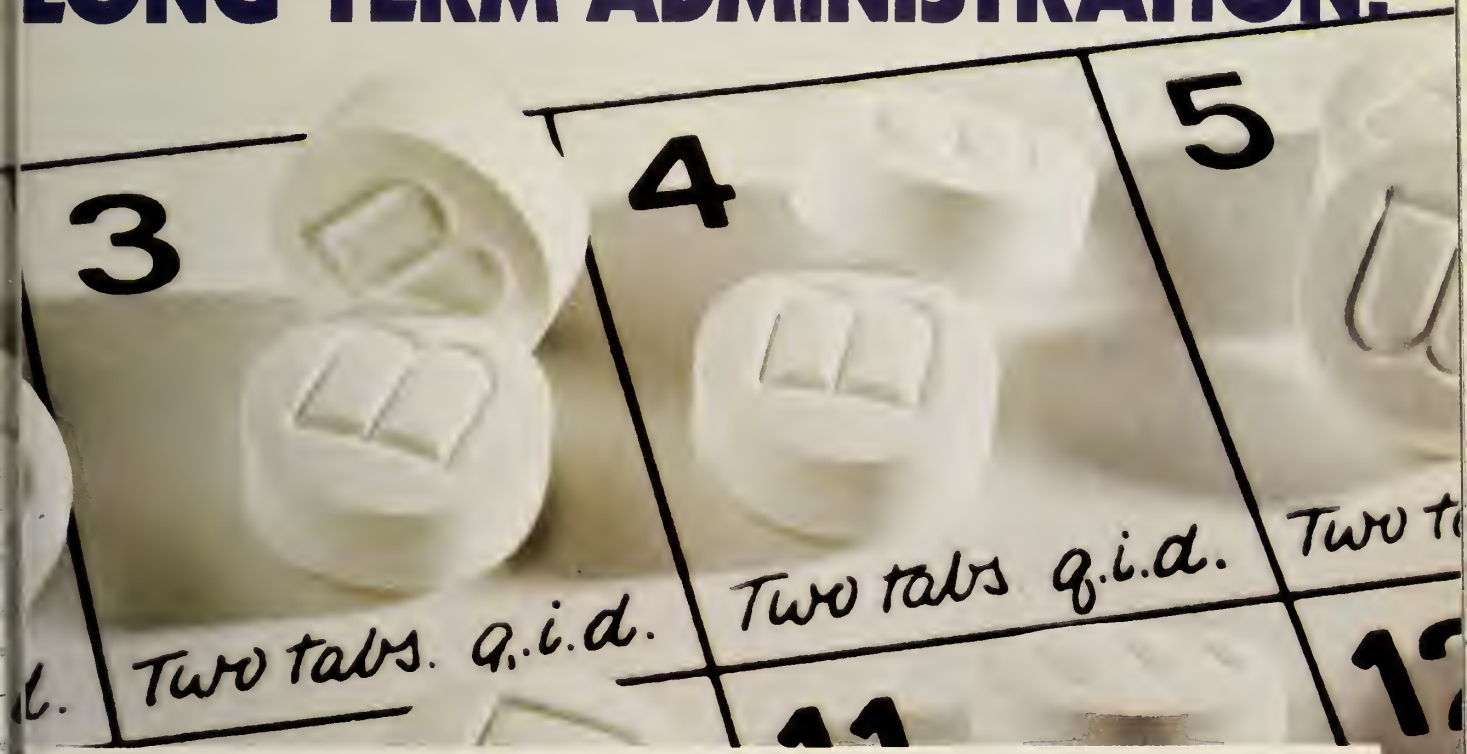

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Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances, anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies Reassess periodically usefulness of the drug for the individual patient

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma

Warnings: Not recommended in primary depressive disorders or psychoses As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants

Physical and Psychological Dependence Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months

Precautions: In depression accompanying anxiety, consider possibility for suicide

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated anxiety agitation, irritability, tension, insomnia and occasional convulsions

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day) Effect was reversible only when treatment was withdrawn within 2 months of first observation Clinical significance is unknown, but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease

Safety and effectiveness in children under 12 years have not been established

ESSENTIAL LABORATORY TESTS Some patients have developed leukopenia, some have had elevations of LDH As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy

CLINICALLY SIGNIFICANT DRUG INTERACTIONS Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol

CARCINOGENESIS AND MUTAGENESIS No evidence of carcinogenic potential emerged in rats during an 18-month study No studies regarding mutagenesis have been performed

PREGNANCY Reproductive studies were performed in mice, rats, and 2 strains of rabbits Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses Clinical significance of these findings is not known However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide

NURSING MOTHERS It is not known if oral lorazepam is excreted in human milk like other benzodiazepines As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%) Less frequent are disorientation, depression, nausea change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken Manifestations of overdosage include somnolence, confusion and coma Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined

Ativan® (IV) for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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Why one benzodiazepine and not another?

Are you concerned about long-acting metabolites? Many clinicians, as well as pharmacologists, are beginning to draw attention to this problem (see New England Journal of Medicine, April 5, 1979).

In contrast to some older benzodiazepines, Ativan (lorazepam) does not give rise to long-lasting active metabolites. As with all benzodiazepines, you should follow the usual precautions concerning co-administration with other CNS depressants and warn your patients against operating dangerous machinery and motor vehicles.

However, it is noteworthy that Ativan showed no clinical evidence of accumulation even when given in high doses over periods up to 6 months. The half-life of free lorazepam is about 12 hours; steady-state serum levels are attained in 2-3 days. Comparable data for diazepam: 20-50 hours and at least 7-10 days. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Ativan has a convenient b.i.d. or t.i.d. dosage schedule; it is compatible with a long list of other medications and, of course, it is a highly effective anxiolytic agent, as established in numerous nationwide, double-blind, controlled evaluations in thousands of patients.

See important information on preceding page.

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for (lorazepam)
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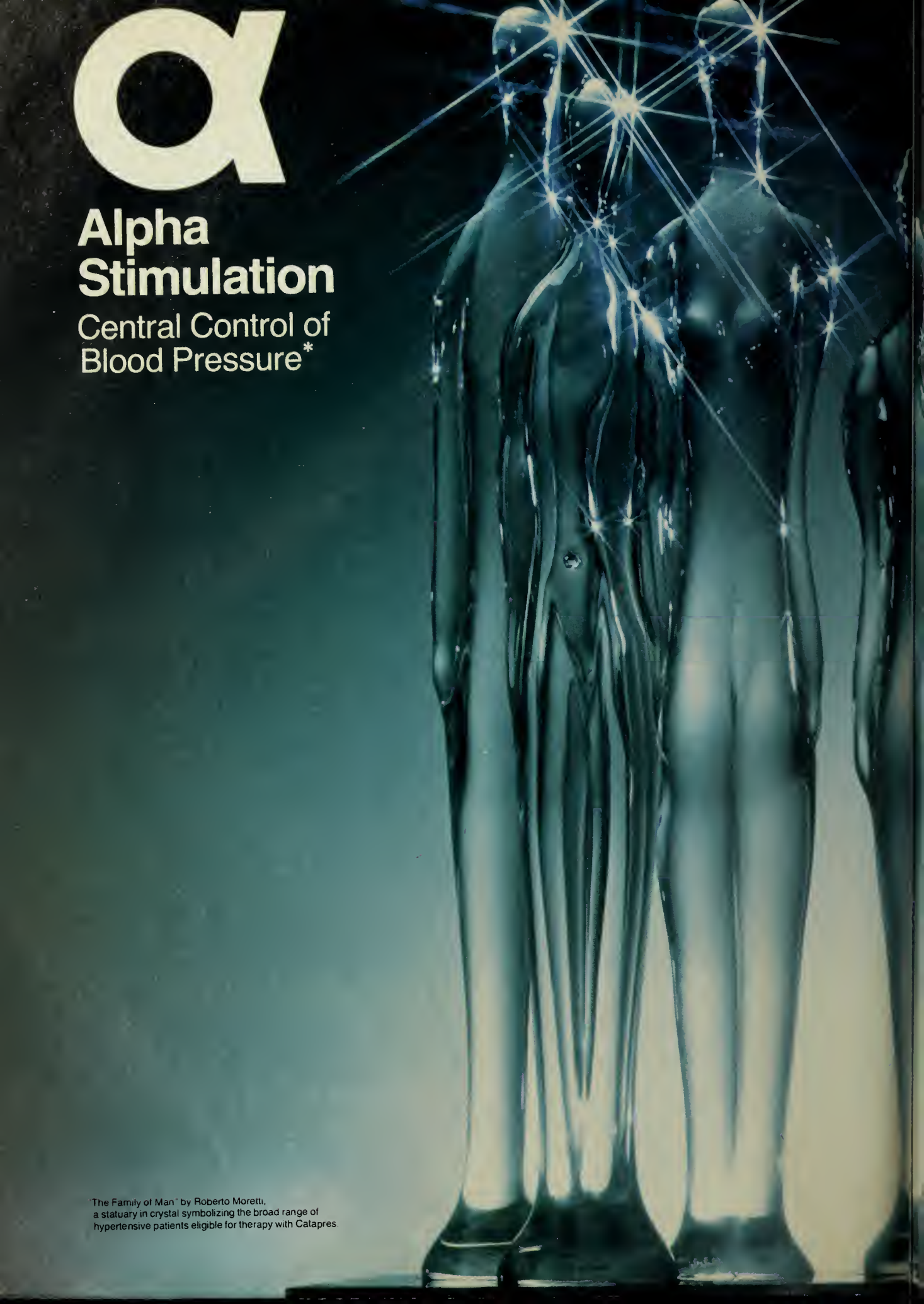
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*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

1. Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

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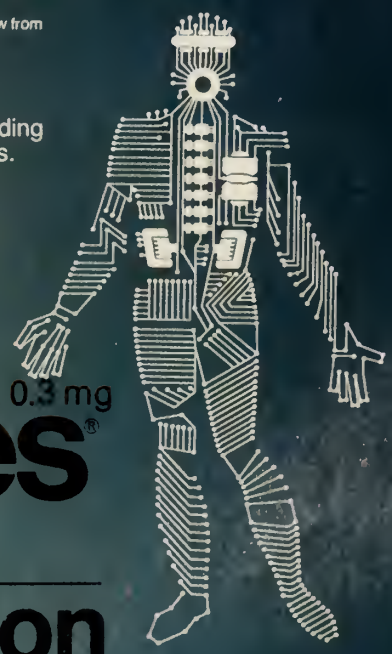

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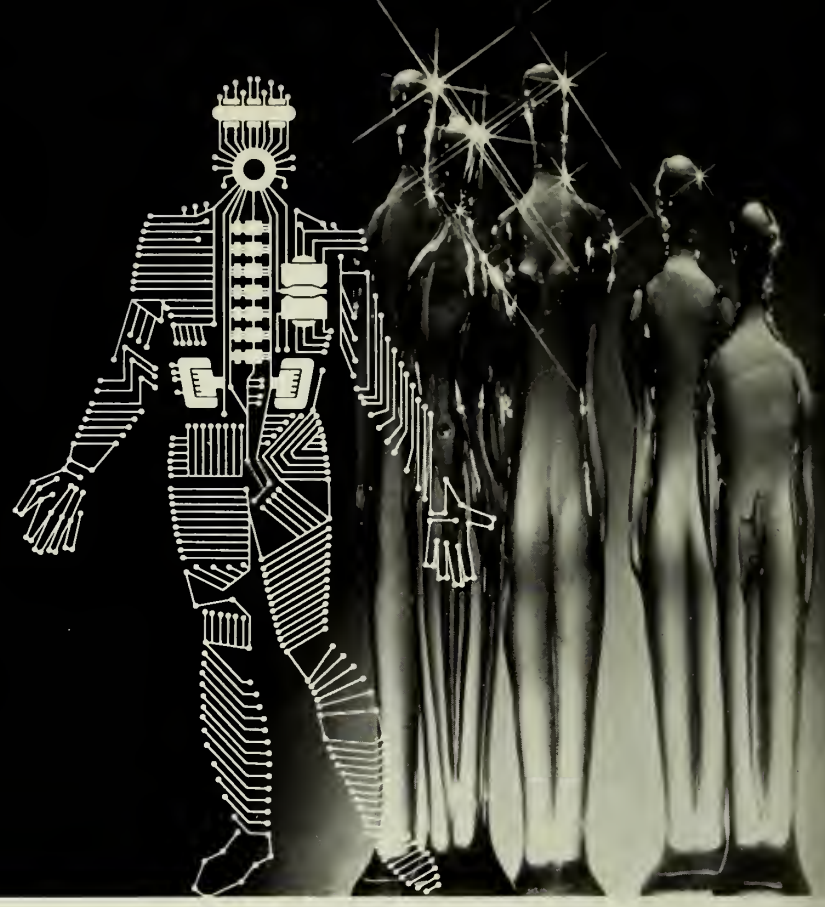

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Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness a sedation. Constipation, dizziness, headache, and fatigue have been report Generally these effects tend to diminish with continued therapy. The follow reactions have been associated with the drug, some of them rarely. (In so instances an exact causal relationship has not been established.) These inclu Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities liver function tests; one report of possible drug-induced hepatitis without icte and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chl thalidone and papaverine hydrochloride. Weight gain, transient elevation of blo glucose, or serum creatine phosphokinase: congestive heart failure, Raynau phenomenon; vivid dreams or nightmares, insomnia, other behavioral chang nervousness, restlessness, anxiety and mental depression. Also rash, gioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associa with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryne itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomas weakly positive Coombs' test, asymptomatic electrocardiographic abnormalit manifested as Wenckebach period or ventricular trigeminy.

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Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

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Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

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*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

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Refer to: Luk KH, Hulse RM, Phillips TL. Hyperthermia in cancer therapy. West J Med 132:179-185, Mar 1980

Hyperthermia in Cancer Therapy

KENNETH H. LUK, MD, R. MICHAEL HULSE, *and*
THEODORE L. PHILLIPS, MD, *San Francisco*

Many malignant cell lines exhibit a therapeutic response to supernormal temperatures. Selective destruction of tumor cells has been observed following moderate hyperthermia (42° to 43°C) in vivo, and tumor eradication by heat has been achieved without normal tissue morbidity. Thermal cell killing appears to be independent of oxygen tension, and the sensitivity of S-phase cells to thermal damage is complementary to that for cellular radiation response. Hyperthermia is therefore a promising adjunct to radiotherapy. At the Claire Zellerbach Saroni Tumor Institute, Mount Zion Hospital and Medical Center, San Francisco, the differential thermal sensitivity of malignant cells is being studied to achieve improved tumor control in patients refractory to more conventional treatments. Preliminary results of a two-year clinical trial indicated increased local objective responses when hyperthermia and radiation were used in combination.

THE THERAPEUTIC EFFECTS of hyperthermia on various types of cancer have been recognized for more than 100 years.[1] In 1893 Coley[2] reviewed the cases of 38 patients with advanced cancer in whom high fevers developed consequent to accidental or deliberate infection of erysipelas; in 12 patients there was complete regression of tumors and the conditions of 19 others improved. Strauss[3,4] used hyperthermia and surgical procedures to achieve improved responses in 250 patients with carcinoma of the colon and rectum. Hot baths were used with good results by Westermark[5] for inoperable cervical cancer and by Goetze[6] for carcinoma of the penis. Hall and co-workers[7] treated 32 patients with carcinoma of the urinary bladder by perfusing the organ with hyperthermic solutions ranging in temperature from 41.5° to 45°C; in 26 patients there was substantial tumor regression and in four patients complete regression of tumors was achieved. Other early reports described a therapeutic action of heat on sarcoma[2,8] and uterine carcinomas.[9]

Hyperthermia has also been used to augment the effects of other cancer therapies. Stehlin and co-workers[10,11] have treated melanoma of the extremities by perfusing the area with blood combined with melphalan. When the perfusate was hyperthermic, a five-year survival of 76.7 percent of the patients was obtained, compared with a five-year survival of 22.2 percent of those without

From the Department of Radiation Oncology, Claire Zellerbach Saroni Tumor Institute, Mount Zion Hospital & Medical Center, San Francisco (Dr. Luk and Mr. Hulse); and the Department of Radiation Oncology, University of California, San Francisco (Dr. Phillips).

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Reprint requests to: Kenneth H. Luk, MD, Claire Zellerbach Saroni Tumor Institute, Mount Zion Hospital & Medical Center, P.O. Box 7921, San Francisco, CA 94120.

hyperthermia therapy. Cavaliere and colleagues[12] used hyperthermic perfusion alone and in combination with surgical procedures or chemotherapy to treat 111 patients with tumors in the limbs; encouraging results were obtained with osteogenic sarcoma and melanoma. These researchers showed that heat can cause tumor regression, and suggested that hyperthermia stimulates an antitumor immune response for immunogenic tumors.

Interest has developed regarding the use of hyperthermia as an adjuvant to radiotherapy. In 1910 Müller[13,14] reported the cases of 100 patients with histologically confirmed advanced cancer who were treated with combinations of diathermy and x-ray irradiation. Of these patients, there was complete regression of the treated lesions in 32 and rapid but temporary improvement in 36. Warren[15] used various combinations of induced fever and roentgen therapy to achieve significant improvement and palliation in 29 of 32 patients with cancer whose conditions were considered "hopeless." In 1948 Korb[16] reported his results using an internal control to compare the response of tumors to x-rays alone and to a combination of x-rays and heat. He treated two separate basal cell carcinomatous lesions of the skin in the same patient with the same radiation dose, but used hyperthermia as an adjuvant to the treatment of one lesion. The tumor which received x-ray irradiation alone showed no response while the tumor treated with both hyperthermia and x-rays regressed completely.

Recently, Brenner and Yerushalmi[17] used hot air jets and microwave diathermy to achieve local tumor hyperthermia before and during x-ray irradiation of six patients in whom there had been no response to conventional therapies. The results were impressive with three complete regressions and two partial improvements. Kim and co-workers[18] treated 36 patients with an assortment of malignant cutaneous lesions, including melanoma, Kaposi sarcoma, mycosis fungoides and two types of lymphoma. These investigators concluded that radiation followed by hyperthermia was more effective than either modality alone and that prolonged benefits were much greater for the combined modality relative to radiation therapy alone.

Thermal Cell Killing

In the early 1900's several investigators showed that fragments of experimental tumors lost the ability to produce tumors in host animals if they were heated to temperatures of 42° to 47°C for short periods.[19-22] In 1903 Jensen postulated that tumor cells are more sensitive to heat than normal cells,[21] and in 1927 Westermark[23] carried out a comprehensive study using the Jensen sarcoma and the Flexner-Jobling carcinoma in rats. Using diathermy, he was able to heat tumors to 44°C in vivo and obtain complete tumor regression without damaging surrounding skin and normal tissue. Crile destroyed S91 melanoma and sarcoma 180 tumors implanted in the feet of mice with thermal treatments that left the foot intact;[24] he was able to obtain similar therapeutic results with several other experimental and spontaneous tumors.[25]

Tumor control and cell damage in vivo can occur with thermal doses which would leave a large proportion of viable cells if heating was carried out in vitro.[25-30] In fact, thermal cell killing in tissue culture is not invariably enhanced for malignant cells.[31-34] One differential thermal response that is consistently observed in cancer cells in vitro is the inhibition of oxidative metabolism by moderate hyperthermia (41.5° to 43°C).[35,36] For example, Cavaliere and associates[37] found that irreversible inhibition of oxygen consumption by Novikoff hepatoma cells occurred after two hours at 42°C, whereas this temperature produced no effect on respiration in normal and regenerating rat liver cells. Dickson and coworkers have observed irreversible inhibition of oxidative metabolism in several malignant cell lines by 42°C hyperthermia, and they have correlated this inhibition with inability to produce tumor implants in hosts.[38-42] The specific characteristics of malignant cells responsible for this differential heat response have not been identified, but the presence of a relatively heat-labile function in the mitochondrial membrane of cancer cells has been suggested.[43-45]

Using light or electron microscopy, Overgaard and Overgaard[46,47] and Muckle and Dickson[10] have studied the histopathology of experimental tumors treated with moderate hyperthermia in vivo. An outstanding feature of in vivo tumor cell response to temperatures of approximately 42°C is a rapid reaction involving cell pyknosis, destruction and lysis. The reaction occurs selectively in tumor cells and appears to result from stimulated lysosomal activity. Overgaard[30] has hypothesized that inhibition of oxidative metabolism without a corresponding decrease in anaerobic glycolysis causes increased production of lactic

acid and consequent acidification of the intracellular and extracellular compartments; this acidification stimulates the acid reaction of lysosomal enzymes and increases lysosomal digestion. Because thermal inhibition of respiration is enhanced specifically in malignant cells, their destruction is selectively increased. It is noteworthy that the lysosomes of Novikoff hepatoma cells have been found to be more labile than those in normal cells.[48]

Environmental factors probably enhance selective in vivo thermal destruction of cancer cells. Decreasing the pH concentration[49,50] or nutrient levels[51,52] of the extracellular fluid can increase thermal cell killing by several orders of magnitude. Malignant tissue shows relatively elevated production of lactic acid under oxygenation[53,54] and hypoxia increases the rate of lactic acid production by a factor of 2 or 3.[55] The interstitial fluid of tumors presents decreased glucose levels and increased levels of hydrogen ion, carbon dioxide and lactate relative to subcutaneous interstitial fluid and blood serum, and these features become more pronounced with increasing hypoxia.[56-60] As might be expected, induction of additional tissue hypoxia by clamping a tumor-bearing limb before heating enhances tumor destruction.[24,61-63] Environmental influences on in vivo thermal response are difficult to evaluate for obvious reasons, not the least of which is the fact that conditions are not homogeneous within a tumor volume and probably fluctuate in complex ways during thermal treatment.

Thermal stimulation of antitumor immune response may also influence tumor regression in vivo. Experimental tumor systems have been used to show that heating a primary tumor can inhibit the growth of metastases[64,65] and contralateral tumors[66] distant from the site of treatment. Based on clinical observations Cavaliere and colleagues[12] and Stehlin and co-workers[11] have suggested that tumor response to hyperthermia may be improved secondary to stimulation of an antitumor immune response. Stehlin[11] reported increased in vitro cytotoxicity of patient lymphocytes toward their own tumor cells following hyperthermic perfusion for melanoma, and suggested that destruction of melanoma by perfusion liberates antigenic material. Mondavi and associates[67] found that the immunogenicity of heat-killed Ehrlich ascites tumor cells was increased relative to those killed by x-ray. Sugaar and LeVeen[68] conducted histopathologic studies on lung tumors heated with radiofrequency diathermy and observed extensive degeneration of tumor vasculature followed by massive infiltration of round cells and lymphocytes; they noted the similarity of this phenomenon with that of acute allograft rejection and suggested its role in tumor regression.

Obviously, in vivo thermal response is a complex function of several factors, and the relative importance of each is difficult to estimate. Fortunately, enough is known of the selective destructive effect of moderate hyperthermia on cancer tissue to enable a therapeutic gain using carefully planned thermal treatments. Continuing improvements in technology are making selective heating of malignant tissue more feasible. This is particularly encouraging to radiotherapists because hyperthermia is a potent radiosensitizer.

Hyperthermia as Adjunct to Radiotherapy

Radiotherapy involves the destruction of malignant cells by various types of ionizing radiation. Treatment by radiation alone may be effective in achieving control of disease; however, several obstacles to local cure often develop. The radiation dose which may be used in a clinic to control cancer is limited by the radiation tolerance of normal tissue within the field of treatment. Occasionally, tumors recur in areas where normal tissue tolerance has been severely compromised by previous irradiation; in these cases, the allowable radiation dose may be so low that tumor control by radiotherapy is unlikely or inconceivable.

Treatment is further complicated by the presence of radioresistant cell subpopulations within malignant lesions. Cells under hypoxic conditions are approximately three times more resistant to radiation than oxygenated cells, and the relative abundance of hypoxic cells within a tumor is a major factor determining the radiation dose necessary for tumor control. Hypoxia provides no protection from thermal killing in vitro[50,69] and sensitizes cells in vivo.[62,63] Thermal sensitivity of cells varies during the cell cycle and contrasts with the variation in radiosensitivity; the S phase is, at once, the most radioresistant and thermosensitive position in the growth cycle.[70-72] Hyperthermia may also sensitize hypoxic cells and S phase cells to radiation.[33,36,62,70,73,74] This remarkable complementary relationship between hyperthermia and radiation allows tumor control with reduced doses of radiation thus decreasing the possibility of unacceptable normal tissue morbidity. Improved rates of tumor control and cure have been re-

ported consistently by investigators using hyperthermia as an adjunct to radiation therapy.*

It must be stressed that improved tumor response to the combined treatment modality is not due solely to the effects of supernormal temperatures on radioresistant cell subpopulations. Hyperthermia has a general effect on mammalian cells of potentiating radiation damage.[33,70,74,80,81] When mammalian cells are irradiated they suffer cumulative damage before being lethally affected. Cells which are not lethally damaged are able to recover by repairing various lesions caused by the treatment. Hyperthermia inhibits cellular repair processes and reduces the capacity to recover from radiation damage.[33,73,82] The net effect is that cell killing by radiation increases with temperature, even for temperatures which produce insignificant thermal killing.[73]

Local Tumor Hyperthermia and Radiotherapy

Thermal cell killing and radiosensitization increase with temperature. Although in vivo thermal cell killing is enhanced in malignant tissue, hyperthermia augments radiation damage in all mammalian cell types. Therefore, it is desirable to achieve fairly selective, differential heating of lesions to be irradiated. Tumor morphology can make this goal attainable. Heat deposited in tissue is dissipated by the flow of relatively cool blood.[83] As blood flow per volume of tissue decreases, so too does this cooling effect.[83,84] Owing to a relatively decreased blood flow, differential heating of tumor tissue relative to surrounding normal tissue is possible.[68] The authors have observed temperature differences of several degrees centigrade between normal tissue at the periphery of a tumor and tissue at the core in spontaneous animal tumors; the magnitude of the heat gradient which can be attained appears to increase with tumor size.

Methods used to induce local tumor hyperthermia in humans must meet several requirements. Generally, it is necessary to deposit energy at depth. A qualitative approximation developed from in vitro and in vivo data is that a 1°C rise in temperature doubles the thermal destruction effect.[25,72] Because small differences in temperature can cause such large differences in response, it is desirable to achieve a homogeneous temperature distribution throughout the tumor volume. Normal tissue must not be heated excessively, and preferential absorption of energy by normal tissue in the treatment area should be avoided. The heating techniques which are most widely used and show the most promise include inductive heating by electromagnetic radiation, heating by ultrasound and capacitive heating using pairs of electrodes. Each of these methods has characteristic advantages and disadvantages.

Radiofrequency inductive heating[85,86] allows induction of hyperthermia at depth with minimal heating of skin and fat. Focusing of energy into a tissue volume is not possible, and differential tumor heating relies on decreased tumor blood flow relative to surrounding normal tissue. As frequency increases to the microwave range, localization of heating improves, but penetration is compromised. Preferential absorption of energy by skin or fat does not occur, but reflection and standing-wave phenomena become important, and burns can result. Microwave diathermy is useful currently for superficial lesions, but special applicator designs will soon allow invasive tumor heating and heating of cavities such as the bladder, rectum and esophagus. Thermal dosimetry is a major problem associated with these heating methods. Metal temperature probes perturb electric fields and distort the heating patterns they would normally produce. Continuous accurate monitoring of temperature is difficult because spurious readings and inhomogeneous heating result from the interaction of the electric field with the probes and their conductive leads. Nonperturbing temperature probes and a technique of noninvasive thermometry are currently being researched and may resolve these problems in the future.

Ultrasound[87] can be applied with single or multiple transducers to obtain varying degrees of focus. Good penetration may be achieved with the correct choice of frequency, and fat is not heated preferentially. However, preferential absorption by bone precludes the use of ultrasound in many cases. Furthermore, ultrasound is not transmitted adequately through air pockets and much reflection occurs at air-tissue and muscle-bone interfaces. Thermometry with conventional probes is feasible. The volume of heating obtainable by ultrasound may occasionally be too limited for therapy.

Radiofrequency capacitive heating[88] is obtained with pairs of electrodes positioned on either side of the volume to be heated. This intervening tissue acts as a resistor and heating occurs as local cur-

*References 17,18,25,46,62,63,75-80.

rents are generated in it. Electrodes can be shaped to specific requirements and the use of multiple electrodes can allow increased localization and depth of energy deposition. Unfortunately, skin and fat are heated preferentially because of their high resistivities. Cooling the electrodes protects the skin, but the amount of intervening fatty tissue limits the power which may be applied. Consequently, this method often is unsuitable for treating persons who are obese. Inhomogeneous resistivity of the volume of tissue being heated may make it difficult to predict thermal distributions; however, conventional thermistors can accurately measure the temperature in the immediate vicinity of the probe.

A few other methods of heating show promise. Hyperthermic perfusion has achieved impressive results with melanoma and osteogenic sarcoma.[10-12] Whole-body hyperthermia can achieve and maintain accurate uniform thermal distribution, but physiological considerations limit the treatment temperature to a maximum of 41.8°C, and, therefore, prolong the duration of hyperthermia required to produce the desired thermal destruction.[89,90] Treatment by either of these methods is relatively complicated, and careful medical supervision of patients for prolonged periods is required. However, both methods have unique advantages and potentials which guarantee their place in the growing arsenal of therapeutic procedures.

Clinical Experience at Mount Zion Hospital, San Francisco

At the Claire Zellerbach Saroni Tumor Institute in San Francisco, hyperthermia as a treatment modality for advanced cancer is being investigated. For several reasons, we have concentrated our efforts on patients with superficial lesions refractory to other therapy. Superficial tumors may be easily observed and they are well suited to quantitative dimensional measurement. Thermometry is simplified by the ease and accuracy with which thermistor probes may be positioned. Heating may be achieved by microwave diathermy, thus reducing the possibility of involving critical tissues in an undesirable thermal response. The location of superficial human tumors facilitates a careful study on the thermal response of spontaneously arising malignant tissues.

Over two years we have used microwave diathermy apparatus operating at 915 and 2,450 MHz to administer 49 courses of local tumor hyperthermia. Of these, 38 courses were combined with radiotherapy; in these cases, hyperthermia was administered immediately after the ionizing radiation. A typical course of hyperthermia (with or without radiotherapy) consisted of six or nine one-hour fractions, delivered on alternate days, three times per week. Thus, six or nine hours of tumor hyperthermia were delivered over two or three weeks. Photographs and caliper measurements of all treated lesions were taken immediately before each treatment.

All of the patients treated were suffering from recurrent or metastatic disease which was not responsive to conventional treatment. The prognosis for survival of these patients was generally poor, so the effectiveness of treatment was judged by local tumor regression. A complete objective response was represented by complete tumor regression. If regression was not complete, but the tumor decreased in volume by more than 50 percent, it was considered a partial objective response. No response was represented by regression of less than 50 percent.

Several conclusions were reached in the study. In agreement with Crile's early report,[14] complete tumor regression was much more probable when radiation was combined with hyperthermia. The complete objective response rate was 42.1 percent for the combined modality compared with 18.2 percent for hyperthermia alone. Hyperthermia produced an objective response in 36.4 percent of the patients whereas a 78.9 percent objective response rate was obtained with the addition of radiotherapy. Hyperthermia enhanced tumor radiation response and complete regression was obtained with radiation doses which would have been subcurative without this adjuvant therapy. It should be emphasized that radiation was almost invariably administered in low doses due to the past treatment histories of most of our patients.

A considerable number of treatments were given for recurrent adenocarcinomas; 30 courses of combined low-dose radiotherapy and hyperthermia were administered to patients with this diagnosis, and 23 objective responses were obtained for a response rate of 76.7 percent. Squamous cell carcinomas also appear to be responsive to combined treatment; in three out of four patients treated there was complete tumor regression. The limited number of treatments administered for other diagnoses prohibits any conclusions

regarding the relative sensitivity of various cancers to these treatments.

Complications occasionally result from hyperthermic treatment by microwave. These are usually minor and consist of erythema and slight blistering. Rarely, rapid tumor necrosis and regression leave an open sore which requires cleansing and dressing. Such complications show the need for careful medical and technical supervision of patients during and after treatment.

Our investigation has shown that hyperthermia can be useful in cancer therapy, particularly in the management of patients with recurrent tumors in areas subjected to previous irradiation.

Conclusion

Cells in central hypoxic regions of tumors resist radiation damage and may be relatively inaccessible to chemotherapeutic agents. The potent action of hyperthermia on cells of this type is one indication of its potential as an adjuvant therapy. Hyperthermia can be useful in the treatment of patients refractory to conventional therapy. If techniques can be developed which selectively sensitize cancer cells to heat (such as tumor acidification) or which increase the relative absorption of electromagnetic energy by tumor tissues relative to surrounding normal tissues, then hyperthermia may become a primary mode of treatment.

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Outpatient Termination of Early Pregnancies Using Syringe and Plastic Cannula

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Using a 50 ml syringe and a Karman-type cannula-curette, outpatient therapeutic abortions were done in 543 women who were not more than eight weeks pregnant. All patients received paracervical block analgesia and atropine was given intravenously to minimize vagal reactions. In five women (0.9 percent) pregnancies were missed by the procedure, and in 13 women (2.4 percent) abortions were incomplete. In only one patient did a significant postoperative pelvic infection occur. Twenty-seven women (4.9 percent) were not pregnant; the initiation of routine urine pregnancy testing reduced the percentage of those who were nongravid. The procedure using syringe and plastic cannula is safe, well tolerated and has reduced therapeutic abortion costs.

THE KARMAN CANNULA is a flexible polyethylene tube which is manufactured in several sizes for use in vacuum aspiration of early pregnancies. The Milex Suction Cannula-Curette (Milex Products, Inc., Chicago) is similar but, in addition, has a plastic obturator (Figure 1) which provides the cannula with more rigidity. This facilitates insertion of the cannula if the cervical canal is not patulous. These cannulas attach to a 50 ml disposable plastic syringe.[1] When the syringe barrel is withdrawn, wings flare in an extended position, allowing a vacuum to be maintained for several minutes (Figure 2). This report summarizes our experience using the Milex Cannula-Curette for termination of early pregnancies in the outpatient gynecology clinic of the Sacramento, California, Kaiser-Permanente Medical Center.

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Patients and Methods

During 25 months ending March 31, 1978, patients who requested therapeutic abortions and who were not more than eight weeks pregnant by menstrual history were given a 30-minute appointment for the procedure. During the last 15 months of the study, a urine pregnancy test was routinely carried out. The procedure was not done if on examination the uterus was larger than normal for eight weeks of pregnancy. Cultures for gonorrhea were done for all patients.

The uterine aspiration was carried out as previously described.[1] All patients received paracervical block analgesia using 7 to 8 ml of 1 percent lidocaine solution injected into each uterosacral area. Also, depending on the patient's size, 0.2 to 0.4 mg of atropine was given intravenously to minimize vagal reactions. A 6 mm cannula was used in women up to seven weeks pregnant and a 7 mm cannula in those up to 8 weeks pregnant. Cervical dilatation was occasionally necessary in nulliparas.

Intrauterine devices were not inserted until the first spontaneous menses after the aspiration. Unsensitized Rh-negative women who were more than four weeks pregnant received Rh immunoglobulin. Prophylactic antibiotics were not given without a history of exposure to gonorrhea. If pathologic examination of the uterine contents failed to disclose chorionic villi, the patient was reevaluated to exclude an ectopic or persisting intrauterine pregnancy.

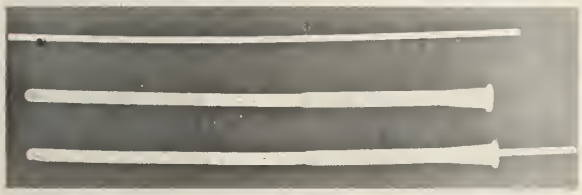

Figure 1.—The Milex Suction Cannula-Curette (Milex Products, Inc., Chicago). Removable obturator provides greater rigidity which facilitates insertion.

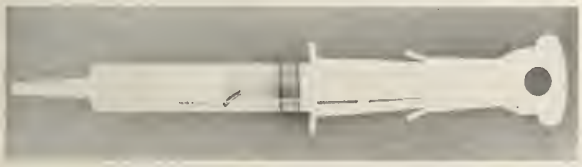

Figure 2.—Plastic syringe (50 ml) which attaches to the Milex Suction Cannula-Curette. Wings flare as syringe barrel is withdrawn to hold barrel in an extended position, allowing vacuum to be maintained for several minutes.

TABLE 1.—*Outcome in 543 Patients Having Clinic Therapeutic Abortions by 50 ml Syringe and Cannula-Curette*

Complication	*Number*	*Percent*
None	483	89.1
Pelvic infections*	11	2.0
Incomplete abortions†	13	2.4
Continuing pregnancy	5	0.9
Abnormal bleeding‡	4	0.7
Not pregnant	27	4.9

*One patient admitted to hospital, five infections mild, five questionable.

†Two released after emergency room vacuum curettage, others admitted to hospital for curettage.

‡Three had curettage, no placental tissue found.

To determine complications, medical records were reviewed for all patients in whom the procedure was done not less than four weeks before. In our closed-panel, prepaid practice, it is unusual for patients to seek medical care elsewhere for significant problems.

Results

During the study, 545 clinic abortions were done by the investigators. Two patients' charts could not be located for review. The outcome and procedure-related complications are summarized in Table 1. There were no known uterine perforations. Of the five women whose pregnancies were missed by the procedure, three were less than ten days beyond the first missed period and two were seven and eight weeks pregnant, respectively. Sixteen women had curettage for abnormal bleeding following the aspiration; 13 had retained placental tissue, but none had pelvic infection. Curettage was not done until three or more weeks after the procedure in ten of the 13 women, as irregular spotting was the only symptom. Normal menses resumed in all patients following curettage.

Eleven patients were treated for postoperative pelvic infection. One, with parametritis, required admittance to hospital. Five of the remaining ten patients had endometritis, and five infections were doubtful as pelvic pain was the only complaint and the diagnosis was not supported by fever or leukocytosis.

Four other patients were admitted to hospital. Two women had attempted suicide, and one required salpingectomy for an ectopic pregnancy two weeks after aspiration of an intrauterine pregnancy. Another had salpingectomy for an asymptomatic hydrosalpinx which was detected when an intrauterine pregnancy, missed by the procedure, was subsequently terminated in the operating room with the patient under general anesthesia.

Infectious hepatitis developed in one patient, but she was not admitted to hospital. Three patients were evaluated for postoperative pelvic pain; however, no diagnosis was made and no treatment given. Only one gonorrhea culture was positive; the patient did not incur pelvic infection despite not receiving antibiotic treatment until five days after the procedure.

Three of the 27 nonpregnant women had

falsely positive urine pregnancy tests. The remainder were not tested. After pregnancy testing became routine, 435 of the last 443 patients (98 percent) who had the procedure were pregnant.

Discussion

The plastic cannula and syringe technique for therapeutic abortion up to eight weeks of pregnancy and for menstrual extraction are identical. The complication rate of the procedure in nonpregnant women is low (1.1 percent).[2] However, current opinion favors avoiding uterine aspiration in women who are unlikely to be pregnant.[2,3] Thus, the initiation of routine urine pregnancy testing in this series of patients was useful. In our opinion, the procedure is technically easier after the sixth week, as cervical softening and straightening of the uterine axis occur which facilitate passage of the cannula. Also, pregnancies are less likely to be missed by the procedure.

The incidence of procedure-related complications in this series, if pregnancies missed by the procedure are included, was 6 percent. Although 15 women (2.7 percent) were admitted to hospital, 14 of the admissions were for less than 24 hours. The most common problem, incomplete abortion, was more frequent than that reported by others using vacuum curettage in a clinic setting for pregnancies up to 12 weeks.[4,5] This may reflect more thorough patient follow-up in a prepaid group practice such as ours rather than an increase in the frequency of incomplete abortion. The percentage was lower, however, than that reported when the Karman cannula was used exclusively up to 12 weeks of pregnancy (2.4 percent versus 5.9 percent).[6]

Free-standing abortion facilities often routinely treat all patients postoperatively with a broad-spectrum antibiotic.[5] Despite our patients not receiving antibiotics routinely a significant pelvic infection developed in only one patient. Our patient population is nonindigent; the low infection rate and infrequency of gonorrhea presumably reflect this favorable socioeconomic status.

Patient acceptance of this abortion method has been excellent. The method has the additional advantage of reducing the risk of cervical injury, as minimal cervical dilatation is necessary. The flexibility of the cannula may also reduce uterine perforation risk. Formerly, all uterine aspirations were done in the operating room with patients under general anesthesia. Currently, 30 percent of therapeutic abortions (15 to 20 per week) are done in our clinic. This procedure has substantially reduced abortion costs and has made operating room time available for other procedures.

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Paraneoplastic Syndromes

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Neoplasms can produce a variety of remote effects on the host; these are referred to as paraneoplastic syndromes. The syndromes may affect any of the systems of the body, may precede or follow the diagnosis of the underlying neoplasm, and may or may not parallel the course of the neoplasm in severity. The diagnosis of and therapy for these syndromes can be challenging to a physician, but successful therapy may bring about worthwhile relief for the patient. In addition, the syndromes and the substances that cause them are sometimes useful in diagnosing and in following the course of certain neoplasms. Perhaps of greater importance, study of these remote effects of neoplasia may shed light on the nature of the neoplastic process itself.

THE RECOGNITION that neoplasms can produce remote effects on the host is not recent. It is over a century since Trousseau described recurrent thrombophlebitis in association with his own gastric carcinoma. However, over the past decade there has been increasing interest in these phenomena. Initially, these remote effects of neoplasia were thought to be uncommon, as indeed some are; others, however, are now known to be of frequent occurrence. The term *paraneoplastic syndromes* is used here as synonymous with remote effects of neoplasia. In some instances the syndrome has been ascribed to production of a hormone by the tumor; in other instances the mechanism remains obscure.

These syndromes are important for several reasons. First, they occasionally aid in the early diagnosis of the neoplasm. Second, the syndromes have aided in the discovery that many (and perhaps most) neoplasms produce hormones or other substances that can be used as tumor markers.[1] These markers are of increasing use in early diagnosis and in following the course of neoplasms during therapy. Third, the syndromes often provide the opportunity for meaningful symptomatic relief, whether or not the neoplasm itself can be successfully treated. Fourth, and perhaps most important, the syndromes have heuristic value. If we understood the precise mechanisms whereby neoplasms produce these remote effects, we would be closer to understanding the nature of the neoplastic process itself.

For further data and references, the reader is referred to the monograph by Waldenstrom[2] and that edited by Hall,[3] as well as recent reviews.[1,4-9]

Endocrine Disorders

Perhaps the most secure method of documenting the production of a hormone by a neoplasm is to show such production in a cell culture. Almost equal in certainty is the finding of an arteriovenous increase in concentration of the hormone in vessels supplying the neoplasm. Immunochemical or histochemical localization of the hormone in the neoplasm is useful but does not prove

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
APUD = amine precursor uptake and decarboxylation
NSILA = nonsuppressible insulin-like activity
PML = progressive multifocal leukoencephalopathy
SIADH = inappropriate secretion of antidiuretic hormone

production as opposed to storage. A greater concentration of the hormone in the neoplasm than in the adjacent tissue helps to rule out the latter as the source of the hormone. Less certain still is the finding of an elevated level of circulating hormone in the presence of a neoplasm derived from a tissue that does not normally produce that hormone; here, there may be a coexisting adenoma of the gland which normally produces the hormone. Subsidence of the syndrome and of the elevated circulating hormone level following resection of a neoplasm is frequently the only available evidence of hormone production by the neoplasm, but these findings do not rule out production by adjacent tissue removed with the neoplasm. Recurrence of the syndrome and of the elevated hormone level in association with distant metastases provides better evidence.

These criteria should be kept in mind when one reads reports of the putative paraneoplastic syndromes. Recent reviews have examined the degree to which the criteria have been met in reports of hormone production by neoplasms.[2,5-9] In general, bioassay of hormones is relatively insensitive but correlates well with clinical effects. Immunoassay is more sensitive but may measure biologically inactive prohormones or hormone fragments as well as active hormones, all of which may be produced by neoplasms.[4] Among the prohormones only progastrin has noteworthy biologic activity.[4] The term ectopic is used to describe production of a substance by a neoplasm derived from a tissue which is not believed to produce that substance under normal conditions.

*Cushing Syndrome**

In 1928, before Cushing's description of the syndrome that bears his name, Brown reported weakness, hyperpigmentation, hirsutism, truncal obesity, edema, hypertension and hyperglycemia in a woman with small cell carcinoma of the lung. Bilateral adrenocortical hyperplasia was noted at autopsy. Since then more than 200 cases have been reported of hypercorticism associated with nonadrenal and nonpituitary neoplasms. Most have been small cell carcinomas of the lung,[1-8,10-12] with occasional cases of lung cancer of other cell types[13] as well as bronchial carcinoids.[11] In addition, there have been scattered cases of malignant epithelial thymoma, islet cell carcinoma, small cell carcinoma of other sites, carcinoids of other sites, and carcinomas of the larynx[11] and salivary glands, medullary thyroid carcinoma,[2] ovarian carcinoma,[2] pheochromocytoma,[6] and possibly other neoplasms. Most of these neoplasms are of the amine precursor uptake and decarboxylation (APUD) series (see below).[2,6] It has been estimated that 15 percent of patients with Cushing syndrome have nonadrenal and nonpituitary neoplasms.

The clinical features[2,4,5,8,11] of hypercorticism associated with nonadrenal and nonpituitary neoplasms usually do not include a cushingoid fat distribution, probably because of the brevity of survival and the cachexia which accompanies most cases. Hyperpigmentation is seen in 23 percent, hypertension in 36 percent, edema in 30 percent, fasting hyperglycemia in 38 percent, and impaired glucose tolerance in 93 percent of cases.[11] A hypokalemic alkalosis is present in 72 percent and can be of life-threatening severity.[11] Laboratory findings[2,4,5,8,11] include substantially elevated plasma cortisol levels, as well as elevation of urinary 17-hydroxycorticoid and (in 33 percent) 17-ketosteroid excretion. The latter may be associated with masculinization in female patients. Diurnal variation in steroid production is absent. Hypernatremia is an occasional finding.

The syndrome is due to production of adrenocorticotropic hormone (ACTH)[4] by the neoplasm which causes adrenal cortical hyperplasia with excessive production of glucocorticoids, mineralocorticoids and androgens. Plasma ACTH levels are usually higher than are seen with overproduction of ACTH by the pituitary.[4] Selective venous sampling can confirm the site of ACTH production but is rarely necessary.[14] In addition to ACTH, most and perhaps all of these neoplasms also produce "big" or pro-ACTH,[4,15] which has little biologic activity. An uncertain percent of these neoplasms also produce corticotropin-releasing hormone (CRH), which stimulates the pituitary to produce more ACTH.[11,16] It is possible that these CRH-producing neoplasms, particularly bronchial car-

*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

cinoids, include the rare cases in which dexamethasone will partially suppress[4] or metyrapone will increase 17-hydroxycorticoid excretion. In most patients, neither dexamethasone nor metyrapone will affect steroid excretion.[11] The hyperpigmentation has been ascribed to ACTH and to β-melanocyte-stimulating hormone (β-MSH), although β-MSH may be an artifact; the compound measured by immunoassay is probably β-lipotropin.[1,4] Nonetheless, hyperpigmentation is important clinically, in that its presence in association with hypercorticism almost always indicates that the syndrome is due to ACTH production (by a pituitary or other neoplasm) and not to a primary adrenal disorder.

Removal of the tumor is possible in only about 10 percent of patients. Hence, palliative therapy is important. Successful radiotherapy or chemotherapy of the neoplasm can alleviate the hormonal syndrome. In addition, therapy directed at decreasing the production of glucocorticoids and mineralocorticoids can bring considerable symptomatic relief.[1,2,4,5,8,11] Mitotane is toxic to the adrenal cortex. Aminoglutethimide inhibits the first step in the production of all corticoids. Metyrapone inhibits 11-β-hydroxylase, thus blocking the production of cortisol, corticosterone and aldosterone. Hence, metyrapone can cause a decline in levels of those steroids which cause symptoms, although in most cases the total steroid excretion remains the same. Spironolactone can block the actions of mineralocorticoids, but large doses may be required. Therapy for hypokalemia, hypertension or diabetes may be necessary as well. Bilateral adrenalectomy is rarely indicated; as is the case with the antihormonal agents, the syndrome will be relieved with the exception of the hyperpigmentation.

Hypoglycemia

One must be careful to define the normal range for blood glucose; in normal women it may fall to 35 mg per dl after a 72-hour fast. More than 200 cases of fasting hypoglycemia have been reported with nonislet cell neoplasms.[17,18] About 42 percent of these have been of mesenchymal origin, including fibrosarcomas, other sarcomas, benign fibromas and mesotheliomas. Another 22 percent were liver cell carcinomas, with occasional examples of adrenal cortical carcinoma, lymphoma, gastrointestinal carcinoma and other carcinomas. Most of the neoplasms were large, ranging from 800 grams to several kilograms, and more than 80 percent were abdominal. Other causes of fasting hypoglycemia include starvation, severe liver disease, and insufficiency of anterior pituitary, thyroid or adrenal cortical function. Symptoms of hypoglycemia include central nervous system abnormalities ranging from confusion to coma, seizures and focal defects. Adrenergic symptoms include sweating, tremor and palpitations, but they tend to be related to the rapidity of the fall in serum glucose rather than to its depth.

It was first supposed that the neoplasms produced insulin or proinsulin, but with a few possible exceptions,[4] this has not been substantiated. In this connection, a source of confusion has been the rare islet cell carcinoma with metastases resembling a spindle cell neoplasm. Because of the large size of these neoplasms, it was proposed that excessive consumption of glucose was the mechanism responsible for hypoglycemia. In rare cases it has been possible to show an arteriovenous glucose difference in vessels supplying the tumor or excessive glucose consumption in vitro.[17] The most likely mechanism in most cases is the production by the tumor of a substance (or substances) with insulin-like activity on bioassay but which is not identical to insulin on immunoassay. This activity is referred to as nonsuppressible insulin-like activity (NSILA) because it is not suppressed by anti-insulin antibodies.[19,20] This NSILA is not abnormal per se and makes up most of the circulating insulin-like activity on bioassay in normal persons. However, its persistence in the circulation at high levels in the presence of hypoglycemia is abnormal. The most readily available test to distinguish islet cell from nonislet cell neoplasms which produce hypoglycemia is to assay for the C-peptide, which is present in proinsulin and is produced by virtually all islet cell neoplasms; it is absent from NSILA. It is also absent in cases of surreptitious insulin injection, but this would be an unlikely consideration in a cancer patient. The NSILA has been tentatively identified with somatomedins; these low molecular weight peptides are produced in the liver and possess both growth-promoting and insulin-like activity.[19,20] Their relation to neoplastic growth is unknown. A final possibility in the causation of hypoglycemia is defective hepatic glycogenolysis. Rare case reports appear to document decreased phosphorylase activity in some liver cell carcinomas and in the adjacent liver tissue, resulting in abundant hepatic glycogen despite severe hypoglycemia. It is possible that this acquired glycogen

storage disease occurs in more cases of liver cell carcinoma than is now apparent.

Therapy includes removal of as much of the tumor as possible, and therapy with irradiation or antineoplastic agents may alleviate the hypoglycemia. Chemotherapy for islet cell neoplasms sometimes results in a transient worsening of the hypoglycemia as insulin is released from dying neoplastic cells. However, this transient aggravation of hypoglycemia is rare in chemotherapy for nonislet cell neoplasms, although such a phenomenon did occur in one case of Hodgkin disease.[17] If antineoplastic therapy is unsuccessful, symptomatic therapy[17,18] may help to prevent severe hypoglycemia. One may employ frequent feedings, glucagon, diazoxide or perhaps glucocorticoids. Continuous glucose infusions are necessary in severe cases. Mithramycin has relieved hypoglycemia in islet cell carcinoma; it would be interesting to try this agent in treating other neoplasms which produce hypoglycemia.

Spurious hypoglycemia may occur in leukemias with high counts of circulating leukocytes. If the blood is drawn into a plain tube and the serum not separated promptly, the cells continue to metabolize glucose. The problem is obviated by separating the serum immediately, or by ensuring that sufficient fluoride is present in the tube to stop metabolism.

Hyperglycemia

Hyperglycemia[21] is not often considered as a concomitant of neoplasia. Starvation, impairment of pancreatic or hepatic function, coexisting diabetes mellitus, or exogenous or endogenous glucocorticoids can cause impairment of glucose tolerance.[5] Such impairment has also been reported in association with glucagon-producing islet cell neoplasms and an enteroglucagon-producing renal carcinoma. Hyperglycemia has been reported in association with a somatostatin-containing islet cell neoplasm, although circulating glucagon levels were also elevated. In addition, impairment of glucose tolerance has been reported in some patients with osteosarcoma.[22] In these patients, a glucose load resulted in an accentuated response of both growth hormone and insulin. This interrelationship deserves further study. Growth hormone might be of some pathogenetic significance in osteosarcoma; the peak incidence occurs during rapid skeletal growth, and patients tend to be taller than average. Hyperglycemia has not been reported in association with prostaglandin-containing neoplasms; however, such an association might be suspected, based on the observation that prostaglandins blunt the insulin response to a carbohydrate load.

Hypercalcemia

Hypercalcemia occurs in about 0.3 percent of patients in a general hospital; of these, about 20 percent have cancer and only 5 percent have hyperparathyroidism. In 10 percent to 20 percent of patients with cancer, hypercalcemia develops at some time;[4] usually it is due to "direct" lysis of bone by osseous metastases. This mechanism is incompletely understood; osteoclast-activating factor, prostaglandins, low pH, and perhaps pressure may each play a role. In addition, hypercalcemia has been reported in hundreds of patients without detectable bony metastases, although it is possible that neither radiographs, radionuclide scans, nor routine autopsies are uniformly effective in detecting bony metastases.

Elevated levels of parathyroid hormone (parathormone) have been reported in a variety of neoplasms.[23-27] The most common of these neoplasms is squamous carcinoma of the lung, with adenocarcinoma and large cell carcinoma being less common and small cell carcinoma rare.[26] Squamous carcinomas of the head and neck region are also relatively common.[25] A wide variety of neoplasms, including mainly carcinomas but also occasional lymphomas and leukemias, has been associated with elevated parathormone levels. In some cases it was possible to establish that the neoplasm produced parathormone in vitro.[27,28] In other cases selective venous sampling disclosed that the source of the parathormone was the parathyroid glands and not the suspected ectopic source. It should be recalled that prior irradiation of the neck can give rise to parathyroid neoplasms. The frequency with which ectopic production of parathormone is a feature of neoplasms has been estimated at high[23] and low[24] levels. Parathyroid "hyperplasia" has been said to be a frequent finding at autopsy of patients with cancer. However, it is defined as a reduction in parathyroid fat; it may represent glandular hyperplasia or simply loss of fat due to cachexia. Further data should clarify the question of how often the hypercalcemia in patients with neoplasms is caused by ectopic production of parathormone. One source of confusion is that some neoplasms produce proparathormone[27] or the inactive carboxy-terminal fragment of parathormone, both

of which may be detected in an immunoassay for parathormone.

Elevated levels of prostaglandins, particularly prostaglandin-E2, have been reported in association with a variety of neoplasms, mainly carcinomas.[27,29-32] Because prostaglandins are widely distributed in normal tissues, it is doubtful that the term ectopic should be used in this connection. Increased concentrations of prostaglandin-E2 and cyclic AMP (adenosine-5-monophosphate) have been found in neoplastic cells;[31] production by these cells is likely.[32] That prostaglandins play a role in the hypercalcemia associated with neoplasms is supported by the relief of hypercalcemia in some patients with the use of the prostaglandin antagonists acetylsalicylic acid and indomethacin.[29,30] Osteoclast-activating factor has been reported in myeloma[33] and similar bone-resorbing activity in acute lymphocytic leukemia[34] as well as in phytohemagglutinin-stimulated normal lymphocytes.[4] As is the case with prostaglandins,[32] it is as yet unclear how often these bone-resorbing factors produce hypercalcemia as a remote effect as opposed to promoting bone lysis in situ. Non-vitamin D sterols have been reported in breast cancer, but have not been confirmed. For uncertain reasons some vasoactive-intestinal-polypeptide-producing neoplasms have been associated with hypercalcemia.[27]

Additional causes of hypercalcemia in patients with breast cancer are estrogen, androgen, progestin or antiestrogen therapy.[27] Whatever the underlying cause, hypercalcemia can be aggravated by immobilization, dehydration, thiazide administration, adrenal insufficiency and hyperthyroidism.[27] Hypercalcemia frequently accompanies paraproteinemia in myeloma and related disorders. Usually this represents a potentially dangerous elevation of ionized calcium. Occasionally, however, the excess serum calcium is entirely bound to the paraprotein, and the ionized calcium level is normal.[35] Therapy for hypercalcemia has been reviewed.[27,35-37] Of interest are the effects of dactinomycin and mithramycin in blocking DNA-dependent RNA synthesis and blocking the effects of parathormone and vitamin D on bone,[38] as well as the effect of glucocorticoids in blocking the action of osteoclast-activating factor[39] and the synthesis of prostaglandins.[40]

Hypocalcemia and Osteomalacia

Hemangiomas[41] and, rarely, other mesenchymal neoplasms may be associated with osteomalacia, hypophosphatemia, bone pain, muscle weakness and renal phosphate wasting. Serum calcium is usually normal, but in one case this may have been due to a coexisting parathyroid adenoma. The syndrome was improved by therapy with vitamin D and phosphate and resolved following removal of the neoplasm. The neoplasm apparently produces a substance which affects the tubular resorption of phosphate.[41] Hypocalcemia is an infrequent concomitant of neoplasia.[37] Medullary carcinoma of the thyroid, small cell carcinoma of the lung, and, occasionally, other neoplasms can produce calcitonin,[42] but hypocalcemia is rare in these patients. Calcium uptake into osteoblastic metastases is an infrequent cause of hypocalcemia.[43] Additional causes include malabsorption, renal insufficiency, hypomagnesemia, hyperphosphatemia, anticancer agents, and destruction of the parathyroid glands by surgical procedure or cancer.[37]

Inappropriate Secretion of Antidiuretic Hormone

Inappropriate secretion of antidiuretic hormone (SIADH) has been reported in over 100 patients with neoplasms.[44-46] In one series of 86 patients with SIADH, 20 had cancer; of these, 14 had lung cancer,[45] usually small cell carinomas. Occasional reports describe the syndrome in patients with neoplasms of the digestive system[45,46] and, in rare cases, with other neoplasms including lymphoma.[4,45] Strict criteria for the diagnosis of SIADH should be kept in mind.[44,45] The syndrome is also present in patients with a variety of benign conditions of the lungs and nervous system.[45] In view of this, plus the fact that the most common neoplastic cause is lung cancer, a question arises as to whether the vasopressin is produced in the neoplasm or as a response to the neoplasm. In some cases,[2,6] production by the tumor has been shown. Additional causes of SIADH includes vincristine, which appears to increase the level of antidiuretic hormone as a neurotoxic effect,[45] and high-dose cyclophosphamide, which appears to exert a direct but transitory effect on the kidney through its metabolites.[45] Other drugs may have similar effects.[44] The symptoms of hyponatremia include confusion and seizures. The therapy for SIADH has been reviewed[44,45] and includes fluid restriction and demeclocycline, which blocks the renal effects of vasopressin.[47] Aggravation of SIADH should be avoided by close monitoring of serum

sodium levels when patients with cancer receive intravenous infusions.

Diabetes Insipidus

Diabetes insipidus can result from destruction of the posterior pituitary by a neoplasm.[45] The condition occurs in 0.95 percent of patients with breast cancer. Metastatic breast cancer is the most frequent cause of diabetes insipidus in women over the age of 60,[45] while lung cancer is the most frequent cause of pituitary metastasis in men. Of patients with metastasis to the pituitary, 7 percent have diabetes insipidus and 1 percent have panhypopituitarism. Of course, these represent direct effects of a neoplasm and are included for completeness. Nephrogenic diabetes insipidus in patients with cancer can result from hypercalcemia, hypokalemic nephropathy, renal amyloidosis and sudden relief of urinary obstruction.[45]

Carcinoid Syndrome

The carcinoid syndrome has been reported in rare cases of noncarcinoid neoplasms, including adenocarcinoma of the pancreas, islet cell neoplasms, small cell carcinoma of the lung, medullary carcinoma of the thyroid, and carcinoma of unknown primary site.[48] Most of these neoplasms originated from cells of the APUD series.

Gynecomastia

Gynecomastia is a frequent finding in nonseminomatous carcinomas of the testis[49] and a rare finding in liver cell[50] and renal cell carcinomas, large cell and other lung carcinomas, and other neoplasms. A careful study of patients with testicular cancer[49] showed that the β subunit of chorionic gonadotropin, prolactin, estrone, and estradiol in various permutations were all correlated with gynecomastia, but each alone could be increased in the absence of gynecomastia or could be normal in its presence. Neoplastic cells[51] and the normal placenta[52] can aromatize C19 androgenic precursors into estrogens. Cirrhosis and drugs such as digitalis, estrogens, phenothiazines and spironolactone can also produce gynecomastia. In addition, gynecomastia has been observed in adolescent males and, rarely, in men treated with antineoplastic agents; presumably this is a result of damage to the androgen-producing cells. A related syndrome is precocious puberty, which has been reported in young boys with hepatic neoplasms which produced chorionic gonadotropin.[53] There is evidence that neoplasms can produce a chorionic gonadotropin lacking in carbohydrate; this compound may be cleared from the blood too rapidly to be detected or to produce biologic effects.[4] This fact may explain why gonadotropin production by neoplasms may be much more frequent than had been appreciated.[1,4]

Hyperthyroidism

Hyperthyroidism is a very rare concomitant of nonthyroid neoplasms.[54,55] Most of these patients had a hydatidiform mole or choriocarcinoma, with isolated instances of nonseminomatous testicular carcinoma. Other patients may have laboratory evidence of thyroid hyperfunction without clinical signs.[2] The syndrome appears to be caused by the thyroid-stimulating effects of chorionic gonadotropin rather than by a separate hormone.[55] With one possible exception,[2] there have been no documented examples of ectopic production of thyrotropin.

Hypertension

Besides its well-known association with pheochromocytoma, neuroblastoma and aldosteronoma, hypertension has been reported in association with renal neoplasms including hemangiopericytoma, Wilms tumor, and renal cell carcinoma.[56] The hemangiopericytomas appear to be derived from juxtaglomerular cells, which produce renin under normal conditions. Hence, they may be regarded as endocrine tumors; the elevated renin levels they produce are not of ectopic origin. The situation with Wilms tumor and renal cell carcinoma is less clear. High levels of renin in plasma have been reported with these tumors; the renin levels and blood pressure may decrease following nephrectomy.[56] In these cases, it seems possible that the renin was produced by the adjacent, compressed renal tissue. However, there are isolated reports of recurrent hypertension with the appearance of distant metastases of renal cell carcinoma.[56] Here it seems likely that the metastases produced renin. There is a report of a renin-containing carcinoma of the lung associated with hypokalemia and hypertension.[57]

Hematologic Disorders

Polycythemia

The upper limit (mean +2 SD) of red blood cell mass as measured with chromium 51 at sea level ranges from 29.6 to 30.6 ml per kg of body weight in women and from 33.9 to 36.5 in men.

Polycythemia, a level above these ranges, has been reported in over 300 patients with neoplasms.[56,58] Most of the these have been renal (renal cell carcinoma or Wilms tumor), with liver cell carcinoma the next in frequency.[56,58] Polycythemia has also been associated with cerebellar hemangioblastoma and with occasional examples of other neoplasms, including leiomyoma of the uterus and others.[56,58] In addition, polycythemia has been associated with such nonneoplastic renal lesions as cystic disease and hydronephrosis. Unlike polycythemia vera, the polycythemia associated with neoplasms is usually not accompanied by leukocytosis, basophilia, eosinophilia or thrombocytosis. Other causes of polycythemia include cardiopulmonary disease, abnormal hemoglobins, and endogenous or exogenous androgens.[56,58] Alveolar hypoventilation should be ruled out in the presence of a brain tumor and carboxyhemoglobinemia in a smoker. Between 1 percent and 5 percent of patients with renal neoplasms have polycythemia, and a similar proportion of patients with polycythemia have a renal neoplasm.[56,58] In a patient with unexplained polycythemia, intravenous urography should be done.

In most of the cases studied there were elevated levels of serum or urine erythropoietin,[56,58] which appeared identical with "normal" erythropoietin. Erythropoietin has been isolated from renal cell carcinoma, Wilms tumor, liver cell carcinoma, cerebellar hemangioblastoma and leiomyoma.[56,58] It has also been isolated from renal cyst fluid,[58] which suggests that, at least in some cases, it is produced by adjacent, compressed renal tissue. However, the recurrence of polycythemia with distant metastases[56,58] shows that neoplasms can produce the hormone. An additional possibility is suggested by a case of liver cell carcinoma with a high plasma level of erythropoietin but with none detected in the neoplasm.[58] This patient's liver tissue lacked the normal ability to inactivate erythropoietin.

Erythroid Aplasia

Severe anemia, absence of reticulocytes and a substantial decrease in erythroid cells in the marrow have been associated with thymoma, usually of the spindle-cell type.[59-62] Perhaps 5 percent of thymomas are associated with pure red blood cell aplasia, and occasional cases are also associated with leukopenia or thrombocytopenia.[61] Conversely, a third to a half of adults with erythroid aplasia will have a thymoma; additional cases have been ascribed to marrow injury by drugs or viruses, or in association with pregnancy. Rare cases have been reported in patients with cancer of the lung, stomach or thyroid, as well as with lymphoid neoplasia.[58,62] The mechanism appears to be immunologic, with an IgG antibody directed against the nuclei of erythroblasts.[5,60,63] Myasthenia gravis is usually associated with other histologic types of thymoma, but occasionally the two syndromes coexist.[62] Erythroid aplasia is an unfavorable prognostic sign in thymoma.[64] However, from 15 percent to 29 percent of patients enjoy prolonged remissions following thymectomy,[60,64] and another 15 percent when thymectomy is followed by steroid therapy.[60] Radiotherapy may be of benefit, while androgen therapy has yielded variable results.

Hemolytic Anemia

Coombs-postive hemolytic anemia is a common finding in patients with lymphoid malignancies; it has occasionally been reported in association with other neoplasms,[5] including carcinomas of the ovary,[65] stomach, colon,[66] lung, cervix and breast.[67] The direct Coombs test is positive, a reticulocytosis is present, there may be slight splenomegaly, and steroid therapy may be partially effective. Thus, idiopathic hemolytic anemia may be closely mimicked. In some instances removal of the neoplasm cures the anemia.[65] It seems likely that a substance produced by the neoplasm evokes antibodies which cross-react with red blood cells.[66] Production by the neoplasm of a substance which is toxic to red blood cells has not been observed in humans. Anemia of a microangiopathic type can occur in association with neoplasms; here, however, the direct Coombs test is negative and red blood cell fragmentation is seen.

Thrombocytosis and Leukocytosis

Thrombocytosis is a relatively common finding in association with neoplasms, although precise figures are not available.[56,68-71] Usually thrombocytosis occurs with metastatic disease, especially with marrow involvement; in this situation it may be accompanied by leukocytosis. Occasionally, thrombocytosis may be associated with a localized neoplasm and may subside after its removal; this phenomenon appears to be more common in renal cancer.[56] The platelet count rarely exceeds 1 million per μl but may reach 6 million.[71] Hemor-

rhagic or thrombotic complications are unusual, perhaps because platelet function is normal. A spurious hyperkalemia may accompany thrombocytosis of any cause. Other causes of thrombocytosis include hemorrhage, splenectomy, iron deficiency, recovery from myelosuppression, vincristine therapy, and various infectious and inflammatory disorders. A thrombocytosis-producing factor has been tentatively identified in animal experiments;[56,68,72] its source is unproved.

Leukocytosis is one of the leukoerythroblastic features of the blood that may accompany marrow invasion by a neoplasm. Leukocytosis, sometimes of an extreme degree,[73] is noted occasionally in patients with neoplasms in the absence of overt infection or tumor necrosis.[56,68,73] Eosinophilia[4,68,73] or monocytosis[74] may also occur. Other causes of leukocytosis include lithium and recovery from myelosuppression. A leukocytosis-producing factor has been tentatively identified in animals,[56,68,72] but whether it is produced by neoplastic cells is not known.[4]

Coagulopathies

Intravascular Coagulation

Disseminated intravascular coagulation (DIC) has been reported with a wide variety of neoplasms.[75-77] The clinical features may include thrombocytopenia and a decrease in coagulation factors including fibrinogen and factors V and VIII. The Quick prothrombin time and partial thromboplastin time are prolonged. Platelet plug formation is inhibited. The result is a tendency toward general bleeding. Erythrocyte fragmentation may be a part of the syndrome, or hemolysis may occur without overt DIC.[75] The neoplasms most frequently associated with DIC include acute progranulocytic leukemia and carcinoma of the prostate, as well as mucin-producing adenocarcinomas.[75-77] In addition, DIC may occur as a result of therapy, which may release thromboplastic substances from leukemic and normal leukocytes,[75] or cancer cells.[78] Mucin can activate factor X[75,76] and, unlike tissue thromboplastin, can do so despite a deficiency of factor VII. In other patients there may be diminished survival of fibrinogen in the absence of symptoms. Fibrinolytic activity may be increased secondarily.[75] Primary fibrinogenolysis is unusual except following prostatic operations, but it may be seen in some patients with untreated carcinoma of the prostate.[75] The therapy of DIC is controversial and not uniformly successful; heparin is sometimes effective,[75,79] and spontaneous improvement may occur. Other causes of DIC include sepsis and transfusion reactions;[75] L-asparaginase can cause hypofibrinogenemia. A positive protamine test is supportive of a diagnosis of DIC, but may also be caused by transfusion, traumatic venipuncture or venous thrombosis.[75] Localized intravascular coagulation can occur in cavernous hemangiomas and can result in findings similar to those in the disseminated type.[68]

Venous Thrombosis

Migratory thrombophlebitis was first described by Trousseau. More frequent is venous thrombosis with the risk of pulmonary emboli. A thrombotic tendency has been noted in association with many types of neoplasms, particularly those of the stomach, pancreas, ovary, lung and colon.[5,8,77,80,81] In contrast to the bleeding tendency in acute DIC, chronic DIC may be associated with a thrombotic tendency.[76,77] It is clear that patients with various types of cancer have a tendency to thrombosis; it is less clear that they have a greater tendency than do patients equally ill with benign diseases, although there is evidence that this is so.[77,80] Mucin can activate factor X, and endothelial disruption can activate factor XII.[75] Thrombocytosis may also play a role. In those cases in which the neoplasm could be successfully treated, the thrombotic tendency did not recur.[75]

Sterile Endocarditis

Sterile vegetations on previously normal heart valves may occur in association with a variety of neoplasms, especially mucinous adenocarcinomas.[5,76,81,82] The valves affected are usually on the left side of the heart, which is difficult to explain if the syndrome is caused by substances released into the systemic circulation. Sterile endocarditis occurs in about 20 percent of patients with chronic DIC, and in those in whom it occurs arterial emboli are frequent.[76] A murmur may or may not be heard.[81] The vegetations are composed of platelets and fibrin; occasionally they become secondarily infected.[82] Thrombophlebitis or overt DIC usually does not coexist with sterile endocarditis. The syndrome is seen with chronic nonneoplastic diseases somewhat less frequently than in association with cancer.[82] However, the term marantic is inaccurate; the patients may not be cachectic.

Dysfibrinogenemia

Acquired structural abnormalities in the fibrinogen molecule have been reported in association

with liver cell carcinoma, as well as with cancer metastatic to the liver and benign liver disease.[83] The result is prolongation of prothrombin, thrombin, and partial thromboplastin times, as well as inhibition of the clotting of normal plasma. There is no evidence of factor deficiency or fibrinogenolysis. In most patients there was no clinically important bleeding.

Protein Disorders

Amyloidosis

Amyloid deposition may be associated with myeloma and macroglobulinemia[84,85] and a variety of nonplasmacytic neoplasms,[56] including renal cell and gastric carcinoma as well as Hodgkin and non-Hodgkin lymphoma. In the past, amyloidosis was divided into primary and secondary types on the basis of the organs involved and the underlying condition. It now appears that whatever the underlying condition the pattern of involvement may be similar and may include the blood vessels, heart, carpal tunnel, tongue, gastrointestinal tract, anus, liver, spleen, joints, skin and kidney.[56,84,85] Impairment of organ function, obstruction or bleeding may occur. Factor X deficiency and fibrinogenolysis have been reported. The amyloid seen in association with plasmacytic disorders resembles the light chains of IgG in structure, while that seen in conjunction with other neoplasms contains the "AA" protein.[86] The idea that the protein abnormality reflects an attempt at defense against the nonplasmacytic neoplasm is supported by the following observation. In a patient with renal cell carcinoma there was a spontaneous regression of pulmonary metastasis but renal failure caused by amyloid deposition occurred.[56] Amyloid occurs locally within medullary carcinoma of the thyroid.

Paraproteinemia

Monoclonal gammopathy has been defined as a narrow band on serum protein electrophoresis; at present the term may include the additional requirement that the protein react with either *k*- or λ-antisera but not both, on immunoelectrophoresis. Besides being produced by plasmacytic neoplasms, monoclonal proteins may occur in association with a variety of other neoplasms,[84,87-91] including carcinomas, sarcomas, lymphomas and leukemias. Sometimes these paraproteins show cold-agglutinin or cold-precipitating activity, or both,[84,92] but in most patients they produce no direct symptoms. They may be associated with amyloid deposition. The possibility of a coexisting myeloma should be kept in mind. Each paraprotein appears to be idiotypically unique. However, the paraproteins show no detectable differences at present which would allow one to distinguish between patients with myeloma or macroglobulinemia, those with other neoplasms, and those with no apparent cause for the protein elevation.[91] The differential diagnosis would have to rest on the degree of marrow plasmacytosis, the presence of osteolytic lesions, and the presence or absence of a nonplasmacytic neoplasm.[87]

In some cases, it has been possible to show that the protein is present (and probably produced) in plasmacytes surrounding the carcinoma,[89] which suggests that it may be an antineoplastic antibody.[91] In other cases, the protein has been shown to possess the ability to bind heparin or clotting factors,[91] a situation that could produce a coagulopathy. Some gastrointestinal cancer cells may possess the i-antigen on their surfaces, which might evoke an antibody that agglutinates red blood cells.[92] Besides the possibility that the protein is an antibody directed against an antigen associated with the cancer, and the possibility of a coexisting plasmacytic neoplasm, one might consider the following possibilities. The protein disorder could have rendered the patient more susceptible to the development of a nonplasmacytic neoplasm. On the other hand, the paraprotein and the cancer could have occurred together by chance; perhaps 1 percent of apparently healthy older persons have a monoclonal gammopathy.[91] The disappearance of the gammopathy following removal of a nonplasmacytic neoplasm is extremely rare. A source of confusion is that paraproteins associated with nonplasmacytic neoplasms may be classified as benign monoclonal gammopathies.

Digestive Disorders

Zollinger-Ellison Syndrome

The Zollinger-Ellison syndrome results from non-β cell adenomas or (in 44 percent) carcinomas of the pancreatic islets or duodenum, with production of gastrins (big, little and "mini") by the neoplasm.[4,93] The gastrins cause excessive gastric acid secretion, which results in single or multiple ulcers of the duodenum or jejunum. In addition, in a third of the patients intractable diarrhea develops, perhaps because pancreatic

and intestinal enzymes are inactive at an acid pH. Multiple endocrine neoplasia type 1 (MEN-1) includes gastrinomas or insulinomas as well as parathyroid and pituitary neoplasms. Another dominant condition, MEN-2, consists of medullary carcinoma of the thyroid, pheochromocytoma and parathyroid neoplasms. Those patients who lack parathyroid neoplasms but who have dermal or mucosal neuromas are said to have MEN-2b or MEN-3. However, there is some overlap between MEN-1 and MEN-2.[94]

About 87 percent of cases of the Zollinger-Ellison syndrome result from neoplasms of the islets. There is some doubt that islet cells produce gastrins under normal conditions;[95,96] however, gastrin production by islet cell neoplasms is not usually thought of as being ectopic. There is at least one case report of the Zollinger-Ellison syndrome caused by gastrin production by a mucinous adenocarcinoma of the ovary[97] and another by a ductal adenocarcinoma of the pancreas.[98] Other causes of fasting hypergastrinemia include atrophic gastritis, antral G-cell hyperplasia, retained antrum, impaired function of the kidneys or small intestine and vagotomy without gastrectomy. Routine therapy for ulcer or diarrhea is ineffective.[93] If removal of the neoplasm is impossible, symptomatic therapy with cimetidine may obviate the need for total gastrectomy. Streptozocin therapy may also be useful.

Diarrheal States

Diarrhea often occurs in the Zollinger-Ellison syndrome as well as in the carcinoid syndrome. Non-β islet cell neoplasms may cause "pancreatic cholera" by producting vasoactive intestinal polypeptide (VIP).[99,100] In addition, VIP production and diarrhea have been reported in rare cases of carcinoma of the lung (mainly squamous), as well as pheochromocytoma and ganglioneuroblastoma.[99,100] However, VIP levels require careful interpretation. Prostaglandins[101] and other hormones[4] may also play a role in diarrheal states. Streptozocin or indomethacin therapy may be useful in some patients. Other neoplasms may cause diarrhea by nonhormonal mechanisms. Villous adenoma (or carcinoma) and polyposis of the colon and rectum can cause massive loss of fluid, electrolytes and protein. Adult celiac disease may be associated with an increased incidence of lymphoma;[102] and association with carcinoma of the small intestine has been suggested. The incidence of malabsorption may be increased in cancer patients as a group, but this has not been proved.[5] In this regard, a toxic effect of chemotherapy or irradiation should be considered, as well as mucosal ulceration or lymphatic obstruction by the neoplasm, and amyloid deposition in the bowel wall.[103]

Constipation has not been accepted as a paraneoplastic syndrome. One case has been reported in which constipation and malabsorption were attributed to enteroglucagon present in a renal carcinoma.

Hepatic Dysfunction

Between 10 percent and 14 percent of patients with renal cell carcinoma, but without hepatic metastases, have abnormalities of liver function including elevation of alkaline phosphatase and glutamic-oxaloacetic transaminase levels, reduction in prothrombin activity, reversal of the albumin:globulin ratio, and elevation of Bromsulphalein (sulfobromophthalein sodium) retention.[56,104] Minimal enlargement of the liver may be present, but results of liver biopsies are within normal limits.[104] In those cases in which removal of the neoplasm was accomplished, liver size and function returned to normal. The mechanism is unknown.

Renal Dysfunction

Nephrotic Syndrome

In perhaps 6 percent of patients with the nephrotic syndrome a neoplasm has or will develop.[45,105-107] The syndrome has been associated with Hodgkin and non-Hodgkin lymphoma,[108] as well as carcinomas of the lung, stomach,[109] colon or ovary. The nephrosis may antedate the discovery of the neoplasm; it has been proposed that unexplained nephrosis occurring after the age of 40 should provoke a search for a neoplasm.[45] In some cases nephrosis is caused by invasion of the kidney by neoplastic cells, renal amyloidosis or renal vein thrombosis.[45,108] In other cases an immunologic mechanism is likely. Antigen-antibody complexes have been identified on the glomeruli;[45,105] such complexes may include carcinoembryonic antigen.[105] Viral antigens have been suggested but not proved. Membranous or lobular glomerulonephritis[45] may be present in some patients and minimal-change lesions in others, particularly those with lymphomas.[108] Whether the minimal-change lesion represents an earlier stage is not known.[108] In most cases in

which the neoplasm could be successfully treated, the nephrotic syndrome remitted.[45,105] In one instructive case, both the lung cancer and the nephrotic syndrome remitted with cyclophosphamide therapy. When both the cancer and the nephrosis recurred, cyclophosphamide therapy caused improvement in the nephrosis despite lack of improvement in the cancer. Cyclophosphamide appeared to exert its antineoplastic and immunosuppressive effects independently.

Tubular Defects

Tubular defects of either the proximal or distal types (or both) have been reported in association with multiple myeloma,[5,45,84,110] as well as with idiopathic light-chain proteinuria. The damage to the tubular cells appears to be caused by deposition of light chains. Potassium-losing nephropathy with lysozymuria has been reported in acute nonlymphocytic leukemia.[45,111] However, it is doubtful that lysozyme (muramidase) is the cause of the tubular defect.[112] Its appearance in the urine may be the result of the defect. A proximal tubular defect is sometimes associated with inappropriate secretion of antidiuretic hormone; the mechanism is unknown.[5] Hypokalemic nephropathy may be associated with diarrheal states, production by a neoplasm of aldosterone or renin, Cushing syndrome or renal potassium wasting.[45] Tubular defects may also be caused by therapy with streptozocin, cephalothin or gentamicin.

Musculoskeletal Disorders

Hypertrophic Osteoarthropathy

Hippocrates described curved fingernails, warm fingertips and swollen feet in cases of "empyema." Since that time, hypertrophic osteoarthropathy has been associated with a variety of benign and malignant diseases of the thorax and, less frequently, the abdomen.[5,113-115] Among neoplastic causes lung cancer is the most prominent, but osteoarthropathy is unusual in small cell carcinoma.[13] Other neoplasms affecting the thorax, whether primary or metastatic, benign or malignant, epithelial or lymphoid,[116] may be associated with osteoarthropathy. Intra-abdominal causes are uncommon and include ulcerative colitis[5] as well as carcinoma. In its mildest form osteoarthropathy involves clubbing of the fingers and toes. In more advanced cases there is periosteal new-bone formation visible on bone radiographs and scans. In other cases there may be thickening of the long bones, metacarpals, metatarsals and phalanges. When these changes are associated with a coarsening of the facial features, the clinical characteristics are indistinguishable from those of pachydermoperiostosis,[117] although some reserve this term for the hereditary condition unassociated with thoracic disease. Indeed, the full spectrum from clubbing to pachydermoperiostosis may be hereditary.[117] In most cases associated with a neoplasm, the osteoarthropathy improved when the neoplasm was removed[114] or successfully treated with irradiation or chemotherapy.[116] Clinical features regress more quickly than radiographic signs.

Various mechanisms have been proposed. Neural factors play a role in some patients. In both neoplastic and nonneoplastic conditions, the osteoarthropathy may regress following section of the vagus on the side of the lesion.[5,118] This fact, plus the fact that atropine does not relieve the syndrome,[5] suggests that the vagus carries the afferent limb of the response. The observation that the syndrome may regress after thoracotomy without resection is unexplained. The fact that osteoarthropathy is sometimes associated with estrogen hyperexcretion led to the suggestion that estrogens are causally related.[114] However, the association is inconstant,[5] and osteoarthropathy is not seen with estrogen therapy for breast or prostatic carcinoma. The increased warmth and blood flow of the extremities has suggested a vascular mechanism.[5,119] Neoplasms can produce an angiogenesis factor which may be of great importance in their growth, but its relation to osteoarthropathy remains unproved; limb blood flow may fall after nonresectional surgical procedures.[5] Lung and other neoplasms may contain human growth hormone,[13,120,121] and patients with osteoarthropathy may have acromegaloid features.[114] However, there is no consistent relation between growth hormone levels and the presence or severity of osteoarthropathy.[13,120,121] The same objection applies in the case of neoplasms which contain growth-hormone-releasing hormone.[13,121] Recently, we observed a patient with a malignant mesothelioma in whom both hypoglycemia and osteoarthropathy were manifested. This case is of interest for two reasons. First, osteoarthropathy is said not to occur in malignant mesothelioma.[113] Second, it raises the question of whether somatomedins may be involved in osteoarthropathy as they probably are in hypoglycemia.[19,20,22] One must grant that hypoglycemia and osteoarthropathy coexist un-

commonly; nonetheless, it would be of interest to study somatomedin levels in patients with osteoarthropathy.

Dermatomyositis

The possible association of dermatomyositis and neoplasia has been widely discussed.[5,113,122-125] In large series of patients with dermatomyositis the incidence of malignant neoplasms has been reported variously as 6.7 percent[123] or 16 percent.[124] As has been pointed out, a prospective study would be required to confirm the association.[125] At present, it appears likely that there is some association, particularly when dermatomyositis appears in men after the age of 40.[4,125] The dermatomyositis usually appears within a year of the diagnosis of the neoplasm. Skin manifestations may include erythema or telangiectases of the periorbital region, upper chest or knuckles. Muscle manifestations include proximal-muscle weakness, atrophy and tenderness; they may occur in the absence of skin findings and be diagnosed as polymyositis. The associated neoplasms[125] have included carcinomas of the breast, lung, ovary, and stomach, as well as leukemias, lymphomas and sarcomas. Interestingly, there appears to be a deficit in cases of colorectal carcinoma.[125] Successful therapy for the neoplasm frequently, but not always, is accompanied by improvement in the dermatomyositis.[4,125] However, in the case of chemotherapy, one must consider immunosuppressive as well as antineoplastic effects. The dermatomyositis may respond to steroid therapy,[125] but the response tends to be shorter than in classic dermatomyositis. An immune mechanism is suggested by reports of both humoral[126] and cell-mediated[127] cytotoxicity. Viral-like inclusions have been reported but not cultured. It has been observed that when dermatomyositis accompanies neoplasms, it is more likely to be associated with a motor neuropathy demonstrable by electromyography.[113]

Disorders of the Skin

A wide variety of dermatoses has been reported to occur in association with neoplasia.[2,5,122,128] Dermatomyositis has been mentioned. It is perhaps the best-studied condition, but its association with neoplasia remains in doubt. Prospective studies would be required to establish clearly the association of these conditions with neoplasia.

Acanthosis Nigricans

Acanthosis nigricans is characterized by hyperpigmentation and papillary hypertrophy in the skin folds of the axilla, groin, face, elbows, knees, inframammary area, umbilicus and elsewhere[2,5,128,129] The syndrome may occur in children in an hereditary form unassociated with neoplasia. In adults it has been estimated to be associated with neoplasia in from 25 percent to 100 percent of cases.[2,5,122] Most of the neoplasms associated with acanthosis nigricans have been gastric or other adenocarcinomas.[2] The skin disorder may precede the diagnosis of the neoplasm by many years[122] and rarely improves with treatment of the neoplasm,[2] casting doubt on a direct relationship. In addition, acanthosis nigricans may be seen in association with obesity,[2] diabetes with insulin resistance, pituitary neoplasms and other endocrine disorders, tuberous sclerosis, and therapy with sex hormones or nicotinic acid. Of interest is a case report in which acanthosis nigricans appeared during therapy with a crude preparation of melanocyte-stimulating hormone, cleared when therapy was stopped, and did not recur during therapy with a purified preparation.[130] This observation suggests that the syndrome may be caused by a relatively small compound (presumably a peptide) present in the pituitary. It should be noted that diffuse hyperpigmentation and not acanthosis nigricans is seen in patients with ACTH-producing neoplasms,[2] although acanthosis nigricans has been reported in rare cases of pituitary neoplasms.

Miscellaneous Dermatoses

Pellagra-like lesions may accompany a carcinoid syndrome because of the excessive uptake of tryptophan by the neoplasm.[128] Porphyria cutanea tarda may be associated with liver cell carcinoma or adenoma.[2,131] In most cases the porphyria and the carcinoma both appear to be related to the underlying cirrhosis; however, in a few cases, the adenoma or carcinoma contained much more porphyrin than the adjacent hepatic tissue.[2] A crusting, pustular erythema of the face and skin folds has been reported in a few patients with mild diabetes and glucagon-producing islet cell neoplasms. Pemphigus vulgaris or bullous pemphigoid may be associated with neoplasia in 12 percent of cases.[2,132] An immune mechanism is suggested by the presence of fluorescent antibodies in some cases, as well as by the fact that many of the

neoplasms were lymphoid.[132] However, as with some other dermatoses, some patients were on long-term corticoid therapy before the diagnosis of the neoplasm was made; the therapy, not the dermatosis, may have been the determining factor in the appearance of the neoplasm.

Nodular panniculitis, sometimes accompanied by polyarthropathy, has been reported in association with lipase-containing adenocarcinoma of the pancreas as well as with pancreatitis.[133] Acquired hypertrichosis lagunosa, a diffuse increase in lanugo hair, may accompany various neoplasms as well as diazoxide therapy.[2,5] Erythema gyratum repens is an unusual, rapidly changing erythema in a "wood-grain" or "zebra" pattern; it is said to be strongly associated with neoplasia.[2,5,122] Acquired ichthyosis may accompany various neoplasms.[2,122] Tylosis, a hyperkeratosis of the palms and soles, has been associated with carcinoma of the esophagus in two families; the condition is dominant.[2] It is doubtful that tylosis is related to neoplasia in any other respect.[2] Multiple sebaceous adenomas have been reported in association with visceral carcinomas.

Neurologic Disorders

Neoplasms may involve the nervous system by direct extension, compression, ischemia, metastases, metabolic disturbances or by remote effects.[2,5,134] Perhaps 10 percent of "strokes" prove to be brain metastases. Because there is no effective treatment for the remote effects, every effort should be made to rule out treatable causes of neurologic dysfunction, including metastases, infection, subdural hematoma, angiitis,[135] carotid stenosis,[136] hydrocephalus and emboli. In addition, one should be alert for metabolic disturbances, including hypercalcemia, hyponatremia, hypoglycemia, hyperviscosity, hepatic or renal insufficiency, anemia, and hypoxia, as well as the effects of endogenous or exogenous corticoids or other agents with potential neurotoxicity.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is characterized by progressive weakness of one or more extremities, dementia, disturbances of gait and speech, visual loss, involuntary movements and seizures.[2,5,134,138] Cerebellar or cord signs are unusual. The symptoms usually begin after the underlying disease is well advanced and progress rapidly, with death occurring in two to four months.[137] The electroencephalogram and radionuclide scan may show bilateral abnormalities.[137] Computerized tomographic (CT) scanning has shown bilateral lesions in asymptomatic children who had received cranial irradiation and intrathecal methotrexate; these treatments can be followed by PML. It seems likely that CT scanning will be useful in the early diagnosis of PML.

PML has been reported in patients with leukemia, lymphoma and myeloma; rarely, it may accompany carcinomas or polycythemia vera.[137,138] In addition, PML has been reported in immunosuppressed recipients of organ grafts, as well as in patients with lupus, granulomatous diseases and, very rarely, in previously healthy persons.[137,138]

The resemblance of PML to viral neurologic diseases of animals and humans led to a search for a viral cause. Papova viruses including the JC and SV-40 (simian vacuolating-40) viruses have been recovered from brain tissue of patients with PML.[139-141] The patients from whom the SV-40 virus was recovered had had no known exposure to monkeys. It is conceivable that they received the virus from early lots of "inactivated" polio vaccine, which may have been contaminated with SV-40. The incriminated viruses contain DNA, but clinical trials of idoxuridine and cytarabine (Ara-C) have been disappointing.[142] Vidarabine (Ara-A) has been effective in the treatment of herpes zoster and herpes simplex encephalitis; trials of this agent in PML are awaited with interest. The viruses which have been incriminated in the cause of PML are oncogenic.[138] Bizarre, dysplastic astrocytes are present in many cases of PML.[137] If successful therapy can prolong these patients' survival, the possibility of the development of astrocytoma will have to be kept in mind. It should be noted that even if a viral cause is established, immune mechanisms may aggravate or perpetuate the damage to the brain.

Limbic Encephalopathy

Limbic encephalopathy is also referred to as subacute encephalomyelitis. It is characterized by a subacute onset of cerebral dysfunction, involuntary movements, ocular and bulbar palsy, ataxia, nystagmus, and sensory and motor neuropathy.[143,144] The bulbar and cord findings may be reminiscent of poliomyelitis.[143] The course is more insidious than is the case in PML. The onset may occur before or after the diagnosis of the neoplasm. The syndrome has been reported with carcinomas of the lung, uterus, breast and other sites.[143] The prognosis is usually poor, but im-

provement occurs in some cases. The mechanism is obscure, but there is some evidence for organ-specific antibodies directed against nerve tissue.[143]

Pontine Lesions

Central pontine myelinolysis is characterized by tetraparesis, ocular muscle palsies, pupillary abnormalities and other bulbar signs.[142] The syndrome has been reported in patients with leukemia and, possibly, with other neoplasms. The syndrome may also occur in patients with alcoholism and pancreatitis.[145] Intravenous injection of pancreatic lipase produces demyelination in rabbits; it would be of interest to look for a possible enzymatic mechanism. Pontine lesions may result from cranial irradiation in conjunction with intrathecal methotrexate therapy or (in one patient) in conjunction with systemic therapy with a nitrosourea.

Cerebellar Atrophy

Cerebellar atrophy includes ataxia of the upper and lower extremities, nystagmus, and dysarthria, often accompanied by involvement of the cerebrum, cranial or peripheral nerves, and long tracts.[146,147] It has been associated with carcinomas of the lung, breast, ovary and kidney, as well as Hodgkin and non-Hodgkin lymphoma.[146,147] The onset is often abrupt and the course progressive, although recovery has been reported.[146] The course of the syndrome usually does not parallel that of the neoplasm. The syndrome resembles the viral disease kuru.[146] Fluorouracil and perhaps vincristine may have toxic effects on the cerebellum. The differential diagnosis may also include alcoholism, myxedema, combined-system disease, multiple sclerosis, and the toxic effects of glutethimide and phenytoin.[146] A related syndrome is opsomyoclonus, which is characterized by acute cerebellar ataxia with ataxic eye movement.[148] It may accompany neuroblastoma. It disappears with successful therapy for the neoplasm; for unknown reasons, it appears to be a favorable prognostic sign.

Myelopathy

A poliomyelitis-like lesion of the cord has been the subject of a few reports.[143,149,150] Most of the associated neoplasms have been visceral carcinomas. Metastases to the cord are usually extramedullary. However, they may be intramedullary, in which case the myelogram is usually normal. Distinguishing such a metastasis from a distant effect of cancer would be difficult.[150] Irradiation and intrathecal chemotherapy can cause cord damage including paraplegia.

Neuropathy

Neuropathy involving cranial or peripheral nerves has been reported in association with a variety of epithelial and lymphoid neoplasms.[3,5,143,151,152] In perhaps 16 percent of patients with cancer a neuropathy will develop. The onset of the neuropathy may precede or follow the diagnosis of the neoplasm and the course of the neuropathy may or may not parallel that of the neoplasm.[143] The neuropathy may be motor, in which case it may resemble amyotrophic lateral sclerosis,[162] or it may be sensory, but in most cases it affects both modalities. The differential diagnosis includes amyloid neuropathy caused by amyloid infiltration of the nerves[153] or by compression in the carpal tunnel. In addition, one may consider neuropathy associated with diabetes, tabes, myxedema, uremia or vitamin deficiency. Vincristine, vinblastine, procarbazine and hexamethylmelamine can cause a toxic neuropathy. Corticoid therapy occasionally may improve the neuropathy even in those cases not associated with lymphoid neoplasia.[143] In some cases, there is evidence of antibodies reacting with nerve tissue,[5,154,155] but it is unclear whether they are the cause or the result of neural damage.[5] There is little evidence for a toxic, vitamin-deficiency, or viral mechanism.[5,143] In some patients axonal degeneration is detectable before symptoms appear.[156]

Some forms of neuropathy merit special comment. Neuropathy is reported in occasional patients with polycythemia vera;[2,143] ischemia may be a factor. Irradiation may cause cranial or peripheral neuropathy as a delayed effect. Neuropathy of the brachial plexus may occur as a remote effect of neoplasia;[157] it may also be caused by neoplastic infiltration or irradiation. Abnormalities of taste may be common in patients with cancer and may in part explain anorexia.[158] Autonomic neuropathy with orthostatic hypotension is a rare concomitant of neoplasia.[5,159]

Myasthenia Gravis

About 10 percent of patients with myasthenia gravis have a thymoma, usually of epithelial or mixed type, and an additional 75 percent have thymic hyperplasia.[160-162] Conversely, in about

30 percent of patients with a thymoma myasthenia gravis will develop. Myasthenia gravis has been reported in rare cases of small cell carcinoma of the lung, other carcinomas and lymphomas;[162] however, coexisting thymic disease was not ruled out in all of these reports. In addition, some of the cases may in fact have represented the myasthenic syndrome. Hence, it is doubtful that myasthenia gravis is associated with nonthymic neoplasms more often than can be explained by chance. It should be recalled that the incidence of other neoplasms is probably increased in patients with thymoma.[163] Of patients with myasthenia gravis, 50 percent to 75 percent benefit from thymectomy, although, occasionally, the myasthenia worsens after surgical operation.[160-164] Neostigmine is usually effective. Antibodies binding to acetylcholine receptors have been identified in myasthenia as well as in some patients with thymoma but without myasthenia.[165] Cellular immunity may also play a role.

Myasthenic Syndrome

Eaton and Lambert[166] described a syndrome associated with nonthymic neoplasms, especially small cell carcinoma of the lung. Unlike myasthenia gravis, this syndrome is usually not accompanied by ptosis or respiratory weakness; the tendon reflexes are often reduced, and repeated contraction initially causes increased (not reduced) strength.[162,166] The last characteristic can be noted on an electromyogram and helps to differentiate the syndrome from myasthenia gravis.[162,166,167] A similar electromyogram is produced by botulism and intoxication with neomycin or magnesium.[162,167] However, no toxin has yet been identified in the myasthenic syndrome. The myasthenic syndrome usually does not respond to neostigmine but often responds to guanidine.[5,162,167] The prognosis of small cell lung cancer is improving; it will be interesting to observe the course of the myasthenic syndrome in patients who survive for prolonged periods.

Discussion

There is no hypothesis that can explain all of the remote effects of neoplasia. Nevertheless, some of the data can be made more intelligible using certain hypotheses. These hypotheses are not necessarily mutually exclusive.

Perhaps the most widely applicable hypothesis is that of genetic derepression. It is believed that somatic cells, including neoplastic cells, contain much of the genetic information which was contained in the zygote. This has been seen in amphibians. Nuclei were removed from renal carcinoma cells of frogs and then implanted into enucleated frog ova. Swimming tadpoles developed in about 5 percent of the experiments.[168] The tadpoles were normal in histologic appearance and contained tissues derived from all three germ layers. Similar results were obtained using nuclei removed from normal intestinal epithelial cells, although the success rate was higher than was the case when neoplastic nuclei were used. These data indicate that, at least in this system, some neoplastic cells contain all the genetic information required to form a complete embryo. In addition, the data illustrate that in the proper environment the malignant transformation is reversible. Obviously, most—perhaps 90 percent—of the genetic information present in the zygote is not needed in differentiated somatic cells.[4] The unneeded information must be repressed. Possible mechanisms for this repression involve histone and nonhistone proteins and nuclear RNA. Failure of the repression mechanism is termed derepression.

It is clear that derepression does not occur in a random fashion. As has been mentioned, specific types of neoplasms are more likely to be associated with specific paraneoplastic syndromes. For example, the production of ACTH is more frequently associated with small cell than with squamous carcinoma of the lung.[13] In addition, ectopic hormone production varies from common (in the case of chorionic gonadotropin) to very rare or unknown (in the case of thyrotropin). Further evidence for the selectivity of derepression comes from experiments with neoplasms in animals, which may be characterized by the presence of RNA species not found in the normal, differentiated tissue as well as by the lack of RNA species which are normally present. In this regard, it should be recalled that no neoplasm of a nonendocrine organ has been shown to produce a steroid hormone de novo,[50] although some neoplasms can aromatize C19 precursors to estrogens.[51] The latter ability is possessed by the normal placenta.[52] Perhaps the complex series of steps that de novo steroid hormone synthesis requires is beyond the scope of even a selective derepression. Moreover, with the exception of prostaglandins, all substances known to be produced by neoplasms and to give rise to hormonal effects are proteins or peptides.[4] Hence, derepres-

sion appears to be concerned principally with the synthesis of peptides.

Closely related to the concept of derepression is that of dedifferentiation. Dedifferentiation could involve arrested differentiation, which may be exemplified by teratomas, as well as unbalanced retrodifferentiation, for which there is little direct evidence. Arrested differentiation is sometimes referred to as "blocked ontogeny," but this term implies an abnormality in embryologic development. Congenital neoplasms such as Wilms tumor may be examples of the latter mechanism, but it would be imprecise to refer to a cancer in an elderly person as being the result of blocked ontogeny.

In addition to dedifferentiation of a cell, one must consider dedifferentiation of a tissue.[7] This concept holds that a tissue may be composed of cells in various stages of differentiation. The less differentiated cells may proliferate in a neoplasm of that tissue, leaving the impression that all the cells had dedifferentiated. Evidence for this concept comes from the finding of minute amounts of chorionic gonadotropin[169] and of placental lactogen (chorionic somatomammotropin) in normal testes. The appearance of large amounts of these hormones in the presence of testicular neoplasms might be caused by proliferation of the hormone-containing (and presumably hormone-producing) cells, rather than by dedifferentiation of cells which did not contain the hormones under normal conditions.[7] Chorionic gonadotropin may also occur in the nonmalignant pituitary and other tissues,[170,171] raising the question of whether its presence is characteristic of malignant cellular proliferation or of proliferation in general.[1,4,170,172] The latter possibility seems analogous to the presence of minute amounts of carcinoembryonic antigen in normal gut secretions and its increase in inflammatory bowel diseases, or to the appearance of α-fetoprotein in the circulation during recovery from hepatitis. There are reports of chorionic gonadotropin becoming transiently detectable after a surgical procedure when it was undetectable before the operation[173] thus suggesting an association with benign proliferation. Of interest in this connection is the finding of ACTH (mainly "big") in the nonmalignant but abnormal lung of a dog exposed to smoke and in patients with chronic obstructive pulmonary disease.[12] In addition, plasma levels of ACTH tend to be inversely proportional to the degree of differentiation in lung cancer.[13] In further support of dedifferentiation of a tissue, is the finding, using the immunoperoxidase technique, that chorionic gonadotropin is present in some, but not all, cells of testicular neoplasms.[174] In addition, when two or more *tumor markers* are present simultaneously, their plasma levels may vary in a discordant fashion,[7] which suggests (but does not prove) that they are produced by different cell lines which have different susceptibilities to therapy. However, these data could be interpreted to suggest that the neoplasm contained cells in varying stages of dedifferentiation. Moreover, islet cell carcinomas may produce chorionic gonadotropin or either of its subunits, none of which is detectable in benign islet cell neoplasms.[171] This observation suggests the dedifferentiation of cells rather than of the tissue as a whole.

A further complication is introduced by the possibility that malignant cells may induce surrounding cells to differentiate along lines they normally would not follow.[175] Conceivably, the latter cells might give rise to some paraneoplastic syndromes. Messenger RNA from a human neoplasm can induce in amphibian ova the synthesis of a polypeptide which reacts with antibodies to both calcitonin and carcinoembryonic antigen.[176] If this observation can be confirmed, it suggests that neoplastic cells may produce, or induce surrounding cells to produce, pluripotential prohormones, which are converted to various hormones depending on the enzymatic content of the cell in question.[176] Tumor-host cell hybridization may occur in vivo and is demonstrable in vitro.[177] Such hybrids may produce gene products of either parent cell as well as gene products not present in either parent cell.[177] Hybridization might possibly explain some paraneoplastic syndromes, as well as the mixture of histologic patterns present in some neoplasms[177] or perhaps some instances of drug resistance. Most intriguing is a report that bacteria isolated from patients with cancer appear to contain (and perhaps synthesize) a protein resembling chorionic gonadotropin.[178] The ramifications of such genetic exchange remain to be explored and verified.

Attempts to explain why certain neoplasms are more likely to be associated with certain syndromes have involved classifications based on the presumed embryologic origins of the neoplasms. Pearse and others[6,7,10,11,179] developed the important concept of the APUD system of cells, which share the attributes of amine content, amine precursor uptake and decarboxylation. These cells

share histochemical and ultrastructural characteristics and include the anterior pituitary, autonomic neurons, adrenal medulla thyroid C-cells, islets, and bronchial and gastrointestinal endocrine cells. It was thought that they also shared a neuroectodermal origin. However, it now appears that the islet cells and the bronchial and gastrointestinal endocrine cells are probably of endodermal origin.[180] The parathyroid glands may be of neuroectodermal origin but do not share the APUD characteristics.[180] It is tempting to assume that, for example, small cell carcinoma of the lung arises from bronchial endocrine cells and, hence, may produce anterior pituitary hormones.[6,7] However, the origin of small cell carcinoma has been disputed;[13,181] even if it does originate in the bronchial endocrine cells, these cells probably do not arise from the same germ layer as does the anterior pituitary.[180] Moreover, ectopic production of parathormone has been reported in neoplasms of all three germ layers.[2,5-9] Hence, attempts to correlate ectopic hormone production with embryologic origin have not yet been uniformly successful, particularly when one considers that a single neoplasm may produce up to eight hormones.[2]

Immunologic mechanisms may be related to some paraneoplastic syndromes such as hemolytic anemia, nephrotic syndrome, and some neurologic manifestations.[4,182-184] Several relationships are possible. The immunologic disorder and the neoplasm may occur together by chance; aging is accompanied by an increasing incidence of both. The neoplasm may expose new or previously hidden antigens such as mucin in enteric cancer or casein in breast cancer.[185] These "forbidden contacts" may evoke immune phenomena.[184] On the other hand, the immunologic abnormality may predispose to the development of a neoplasm, as is the case with immunosuppressive therapy. Finally, the immunologic disease may be a temporarily successful host defense against the neoplasm, with cross-reactivity against normal tissues;[184] ulcerative colitis and Hashimoto thyroiditis are possible examples of this mechanism, but direct evidence is lacking.

Another mechanism which has been suggested is random peptide synthesis—that is, that neoplastic cells assemble amino acids at random, sometimes producing a functional peptide by chance. It is most unlikely that neoplastic cells could fortuitously synthesize enough of even a small peptide to have a clinically apparent effect. In addition, if this mechanism existed, one would expect to find peptides with biologic effects similar to those of existing hormones, but which differed substantially from them in amino acid sequence. Such peptides have not been found.

The production of chorionic gonadotropin merits further comment, in that it may shed light on the "fetal" nature of neoplasia. When only insensitive assays were available, this hormone was detected in patients with trophoblastic disease and germinal neoplasms, as well as in pregnancy. As more sensitive assays were employed, chorionic gonadotropin was reported in association with a variety of neoplasms.[186] When still more sensitive assays were used, the hormone was found in association with many, and perhaps even all, neoplasms.[1,4] The synthesis of each subunit appears to be under the control of a separate gene.[187] The α subunit is virtually identical in chorionic gonadotropin and in follicle-stimulating hormone, luteinizing hormone and thyrotropin, whereas each hormone contains a distinctive β subunit.[1,4] These facts only partially explain why neoplasms are so often associated with chorionic gonadotropin and so rarely (if ever) with the other three glycopeptide hormones.[1,4]

The association of chorionic gonadotropin and other "embryonic" proteins with neoplasia is fascinatingly (and perhaps embarrassingly) reminiscent of Beard's "trophoblastic theory" of malignancy, which dates to 1902[188] and may have been based on still earlier work of Conheim. Beard held that "wandering germ cells of early life could later be activated to divide and produce trophoblast cells which, outside the canalization of pregnancy, are the malignant cells." It is no longer believed that all cancers are derived from such cells. Recent data regarding chorionic gonadotropin, however, suggest that many somatic cells—and perhaps all which are capable of replication—carry within their "genetic library" the information needed to reactivate embryonic mechanisms and, under proper conditions, to produce a neoplasm.

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Specialty Conference

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Presented February 9, 1979, at Children's Hospital and Health Center, San Diego.

Vascular Compression of the Upper Airway in Children

J. DEANE WALDMAN, MD:* *In the past 18 months we have seen ten children with upper airway obstruction due to vascular anomalies. In view of the rarity of this condition and the number of different specialties involved in the care of these children, we thought it would be instructive to have a symposium on the subject of vascular compression of the upper airway. Each of the participants has been asked specific questions within his area of expertise. It is hoped that these are the type of questions that a physician with such a patient would ask.*

Dr. Eli Meltzer is both a pediatrician and an allergist; he was asked "How do I recognize one of these children?" Dr. Ken Miller, pediatric radiologist for the Children's Hospital, was asked "What does radiology have to offer in the evaluation of such a child?" Pediatric pulmonologist Dr. Sung Park was saddled with a deceptively simple query: "What is the pathophysiology of obstruction of the upper airway?" As cardiac consultant, I have carried out the invasive studies in these patients and, therefore, my topic will be the differential diagnosis. Dr. John Lamberti is a cardiovascular surgeon with extensive experience in congenital anomalies; he will discuss surgical procedures employed in children with vascular compression of the upper airway.

Clinical Data

ELI O. MELTZER, MD:† At the weekly CPC's at the University of Pennsylvania, there was an elderly clinician who regularly attended and regularly suggested kala-azar in the differential diagnosis of all conditions. Now even in Philadelphia, kala-azar is uncommon. Apparently, the physician wanted the students to note two things: (1) he was the only person who was right the one time that kala-azar was the correct diagnosis and (2) a not so subtle reminder of the old clinical saw "you have to keep a high index of suspicion." To continue our saga of medical homilies, there is the admonition that "when you hear hoofbeats, don't think *only* of horses."

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Today's conference is about some zebras, so to speak; about entities that may cause wheezing but are not asthma, about vascular obstruction of the upper airway. But these zebras are not all that rare, for we have seen ten cases here in San Diego within the last 18 months.

In reviewing the clinical histories of this group of children, certain points became evident. All were products of normal gestations and had normal birth weights; of note is the fact that all but one grew well (Table 1). Despite the presence of a fixed congenital obstruction, the clinical features were highly variable. The pattern was chronic, intermittent with mild-to-moderate (rather than severe) distress; wheezing or stridor and often both were noted, usually with a neonatal or early infant onset of symptoms (Table 1). Recurrent pneumonia was common. A history of swallowing difficulties, especially with solid foods, was occasionally a clue to a fixed, structural disorder of both the esophagus and trachea. In addition, some children were prone to recurrent aspiration pneumonitis.

Findings on physical examination frequently were unremarkable except for large airway noises, variable in nature. Indeed, other than locating the site of difficulty, physical examination was usually of little diagnostic help. Roentgenograms of the chest or bronchoscopy frequently pointed to the vascular system or at least to a discrete extrinsic compression of the upper airway.

The oldest child in our series (5 years old at presentation) had chronic cough and recurrent pneumonia. Wheezing had been reported frequently in the past. On pulmonary function studies, large and small airway obstruction was noted which did not change acutely when epinephrine was given or chronically with prednisone therapy. These results suggested a fixed, large airway disorder subsequently confirmed to be a vascular ring.

One final lesson should be derived from the clinical data. In pediatrics we are all trained to integrate abnormalities into a single disease entity because children very rarely have two separate but concomitant problems. In one of the two girls in our series (patient 1, Table 1) there was a strong family history of atopy; wheezing with and without infection, recurrent otitis, rhinitis and pneumonia were present, as well as both gastrointestinal and respiratory symptoms. She was intolerant of cow's milk, had eosinophilia and documented reaginic activity. In short, there was one very obvious cause of the recurrent respiratory distress: allergic hyperreactive small airway disease. Nonetheless, she *also* had a vascular ring; following surgical operation prominent clinical improvement was noted.

In conclusion, one must amend our old adage to say "When you hear hoofbeats, think of both horses and zebras, remember that they each have various species which can even run together."

Radiologic Evaluation

KENNETH E. MILLER, MD:* In evaluating possible vascular compromise of the airway, radiologists must evaluate three areas in stepwise fashion: (1) the great vessels on plain films, (2) the tracheal airway using magnification film technique[1,2] and (3) the esophagus on a barium swallow.

The Great Vessels

In plain films of a patient with obstructive airway disease, the presence of a right aortic arch suggests the possibility of vascular ring. In a normal child, the trachea is deviated slightly to

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TABLE 1.—*Clinical Characteristics of Children With Vascular Compression of the Upper Airway*

Number	*Diagnosis*	*Age at Presentation*	*Episodes of Pneumonia*	*Other Symptoms*
1. . .	Right arch/left ligamentum	4 m	9	Wheezing; rhinitis, otitis, swallowing difficulties
2. . .	Right arch/left ligamentum	1 w	1	Stridor; wheezing
3. . .	Right arch/left ligamentum	5 y	4	Cough; wheezing
4. . .	Right arch/diverticulum of Kommerell	8 m	1	Stridor; swallowing difficulties
5. . .	Innominate artery syndrome	3 w	0	Stridor
6. . .	Innominate artery syndrome	1 m	0	Stridor
7. . .	"Innominate artery syndrome"; tracheal stenosis	3w	4	Stridor; wheezing
8. . .	Ectopic thymus	2 w	2	Severe stridor
9. . .	Pulmonary artery sling	3 d	0	Stridor; wheezing
10. . .	Tetralogy of Fallot with absent pulmonary valve	1 d	2	Wheezing; failure to thrive

d = days; w = weeks; m = months; y = years

the right on the frontal roentgenogram; a soft tissue shadow to the *left* of the trachea just above the level of the bifurcation is the normal left arch. Tracheal deviation to the left is always abnormal[3] and the presence of a *right* paratracheal mass is the clue to a right arch (Figure 1A). In addition, usually a portion of the descending aorta can be seen behind the heart and adjacent to the vertebral bodies on well penetrated frontal films. Occasionally, the side of the aortic arch may be unclear, especially if the trachea is in the midline, surrounded by equal bilateral soft tissue masses; this may indicate the presence of a vascular ring with double arch (Figure 1B).

Magnification Films

High kilovoltage filtered magnification films[1,2] of the upper airway (Figure 1A,G,I) are taken routinely in children with symptoms of airway obstruction. This technique provides more reliable and accurate information with less radiation exposure than conventional films. These films are taken primarily to evaluate intrinsic causes of airway obstruction, such as epiglottitis, croup, foreign body, congenital web or stenosis, hemangiomas, goiter and the like; these conditions are much more common than vascular compromise. In our experience, anterior displacement and bowing of the trachea on lateral films of the chest (Figure 1F) are more reliable indicators of an aortic arch vascular abnormality than is indentation of the anterior surface of the trachea.

Fluoroscopy

Fluoroscopy has proved of limited help and can be carried out in conjunction with esophagography. One can obtain information about airway dynamics such as ballooning of the hypopharynx during inspiration—indicative of airway obstruction. Tracheomalacia and laryngomalacia can be evaluated with fluoroscopy[4] although both are difficult to confirm.

Indentation of the anterior surface of the trachea may indicate vascular ring, aberrant innominate artery or aberrant left common carotid artery. In addition, such an indentation is present in a surprisingly large number of asymptomatic infants (Figure 1G).[5,6] According to MacDonald

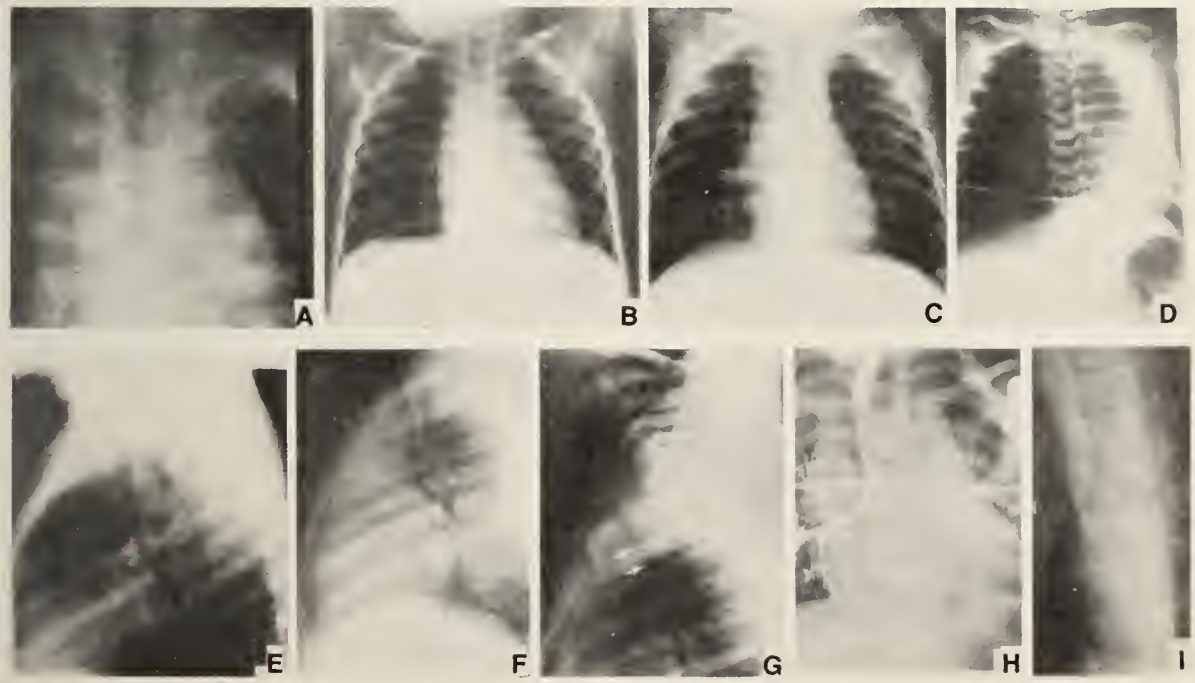

Figure 1.—Roentgenograms of the chest and upper airway. Situs of the aortic arch may be found on the right **A,** easily visible in high kilovoltage films of the upper airway or may be on both sides of the trachea **B,** as in double aortic arch. Pulmonary artery "sling" may produce bilateral air trapping **C,** or may affect only the right side **D,** and can be suggested on the plain chest film—lateral view **E,** by a mass between the trachea and the esophagus. Lateral chest films may show anterior bowing of the trachea **F,** cause by the aorta, diverticulum of Kommerell, or aberrant subclavian artery, or can demonstrate the *normal* airway narrowing seen as the trachea enters the lung. **G,** *Intrinsic* deformities of the trachea can simulate vascular compression: bronchogram **H,** shows generalized tracheobronchial narrowing in a patient initially thought to have "innominate artery syndrome"; high kilovoltage films in the same patient **I,** adequately show the tracheobronchial air column without instillation of lipiodol.

and Fearon[7] anterior indentation of the thoracic trachea should be evaluated by bronchoscopy, looking for a pulsating (presumably vascular) mass; in our experience, this has been frequently unrewarding.

Barium Swallow

The esophagogram provides essential information in the diagnosis of vascular anomalies. The following abnormalities should be sought: (1) oblique indentation made by aberrant right or left subclavian artery, (2) right or double aortic arch confirmation—the S sign on an esophagogram and (3) a mass between the trachea and esophagus—aberrant vessels such as a pulmonary vascular sling or nonvascular masses such as bronchogenic cyst, esophageal duplication cyst or hilar lymphadenopathy. Barium swallow also identifies tracheoesophageal fistula and gastroesophageal reflux, both of which can be associated with chronic aspiration producing reactive airway spasm which can simulate vascular compromise of the upper airway.

Esophagography in small children is potentially dangerous and should be carried out with oxygen, suction and intubation devices ready for use. Either a nurse or a member of the pediatric medical staff should be in attendance during the examination to feed and observe the child during fluoroscopy and to initiate any emergency procedures. We have avoided immobilization of the infants on rigid boards during these procedures preferring to maintain mobility of the child. When stressed, many infants with vascular ring abnormalities need to hyperextend their necks in order to breathe; this is not possible when a child is rigidly immobilized.

One rare situation can be misleading at esophagography; a right aortic arch may be associated with an aberrant left subclavian artery originating from an aneurysmal dilatation of the left descending aorta[8]: the so-called diverticulum of Kommerell (Figure 3B). This posterior mass is larger than the subclavian artery and may be misdiagnosed as a bronchial cyst, enlarged lymph node or esophageal tumor rather than a vascular mass. The diverticulum is frequently as large as the aorta and may displace both the trachea and esophagus anteriorly.

Simple aberrant right subclavian artery with normal left aortic arch is common (one in 200 autopsies) and usually asymptomatic and incidental. Most authorities regard it as an unlikely cause of feeding symptoms, the so-called dysphagia complex.

Mass Between Trachea and Esophagus

A mass located between the trachea and the esophagus (Figure 1E) causing upper airway obstruction can be seen on a lateral plain x-ray film of the chest in the pulmonary artery "sling." The aberrant course of the left pulmonary artery may compress the trachea above the bifurcation obstructing aeration of both lungs (Figure 1C) or, more commonly, may pass around the right mainstem bronchus causing a ball-valve phenomenon in the right lung producing unilateral emphysema (Figure 1D).

In summary, radiologists should look for the right or double aortic arch, and must exclude intrinsic causes of airway obstruction, evaluate the trachea and esophagus for aberrant vessels, and rule out reflux or tracheoesophageal communication as a cause of aspiration and airway

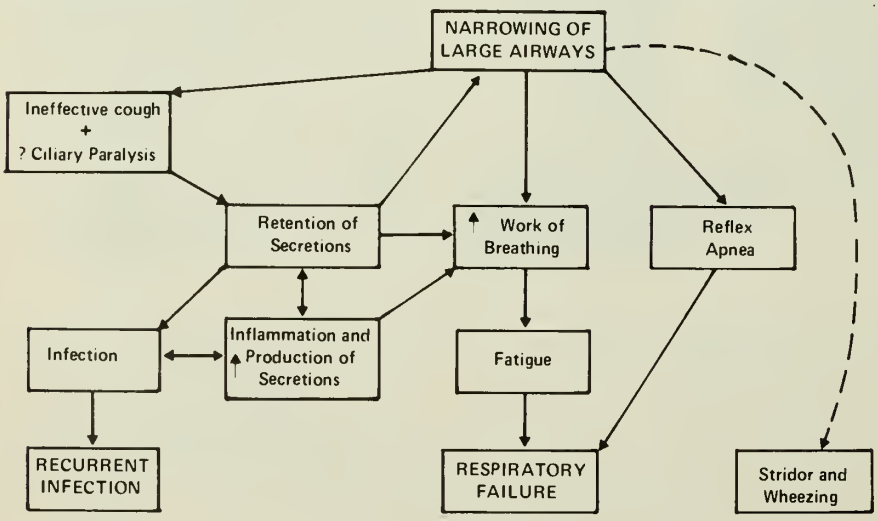

Figure 2.—Pathophysiology of narrowing of the upper airways.

compromise. We have been impressed with our inability to define anterior tracheal compromise in patients with proven vascular rings. We accept a right arch, aberrant (retroesophageal) left subclavian artery and clinical evidence of tracheal obstruction as prima facie evidence of a vascular ring. Close approximation of the trachea and esophagus during esophagography is a good indirect clue of a compressing vascular ring.

Pulmonary Pathophysiology

SUNG MIN PARK, MD:* Narrowing of the large airways can produce three results: (1) recurrent infection, (2) respiratory failure or (3) stridor and wheezing without clinical distress. The pathways from airway obstruction to the serious endpoints can be complex and are interrelated (Figure 2).

Respiratory Defense Mechanisms

Analyzing first the left-hand side of the diagram, we must briefly review the defense mechanisms available to the respiratory tract. There are four basic categories of respiratory defense: (1) mechanical, (2) immunological, (3) biocidal and (4) chemical. These mechanisms tend to work both in parallel and in series; therefore, one system can partially compensate for another. However, if one area is truly malfunctioning, compensation cannot continue indefinitely and the system breaks down, resulting in respiratory infection. For example, no matter how good the mechanical defense mechanism is, repeated respiratory infection occurs if the patient has immune deficiency disease. Another example is the patient with vascular obstruction of the upper airway, who tends to get recurrent respiratory infections although other defense components may be completely normal.

The Cough

Mechanical defenses include nasal air-conditioning, upper airway closure, mucociliary apparatus and cough. Although some authors believe that narrowing of the large airways itself can cause ciliary paralysis,[9] this remains unproved. The cough is one of the most efficient mechanisms to keep the lungs clear of secretions and foreign material. Let us review the dynamic events that occur in the large airways during the cough.[10] The tracheal lumen will reduce to a sixth of the original size with a cough producing a pronounced increase in the linear speed of the air stream. In patients with no obstruction, the reduction of tracheal lumen will leave enough space for the air stream to carry away the secretions. The cough can fail when one or more of the following conditions are present: (1) inadequate volume, (2) failure to trigger, (3) failure to achieve pressure and (4) airway collapse (failure to maintain patency) at the time of cough. With a vascular ring, the patient would have inadequate volume because of the stenosis, but would have normal trigger mechanism by the cough reflex. The pressure generated by the cough would also be insufficient because airway narrowing can restrict the inspiratory volume. Most important, however, the already narrowed airway would completely collapse, making the cough ineffective beyond the point of stenosis; thus, secretions will accumulate leading in turn to inflammation.

Recurrent Infection and Respiratory Failure

Returning to our general schema (Figure 2), we see that ineffective cough leads to retention of secretions, which in turn fosters infection, promotes inflammation and increases the work of breathing. All of these factors can lead to repeated clinical difficulties but infants are especially vulnerable. The infant airway caliber is, by nature, small and the cartilages of the airway are not as rigid as in older patients and therefore are easily compressed. Furthermore, the muscle reserve is considerably reduced in infants. The concept of muscle reserve is very important in understanding respiratory failure. Despite the presence of a pathologic condition in the lungs such as airway obstruction, as long as the patient has sufficient muscle reserve to overcome the added resistance, respiratory failure will not develop. On the other hand, if the patient does not have enough muscle or energy reserve to deal with the increased respiratory work induced by even mild airway obstruction, respiratory failure will occur quickly. Immaturity of the immune system in young infants puts them at a further risk.

Reflex Apnea

There is one other mechanism that can lead to acute respiratory failure: reflex apnea. MacDonald and Fearon[7] reported this occurrence in 50 percent of their patients with innominate artery syndrome in whom surgical operation was required. We have recently seen a patient who had an enormously enlarged left atrium compressing

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TABLE 2.—*Cardiovascular Causes for Compression of the Upper Airway*

AORTA
Double arch (patent or atretic limb)
Right arch
Retroesophageal aorta
Aberrant left subclavian artery
Left arch
Right ductus arteriosus
Aberrant brachiocephalic arteries
PULMONARY ARTERY
"Sling" (left pulmonary artery from right pulmonary artery)
Tetralogy of Fallot with absent pulmonary valve
LEFT ATRIUM
Large left-to-right shunt
Left atrioventricular valve regurgitation
Left atrioventricular valve stenosis

the large airways. His only complaint was of recurrent apneic spells. Therefore, either fatigue from increased work of breathing or reflex apnea can lead to respiratory failure.

Differential Diagnosis

J. Deane Waldman, MD: Before understanding the subject under discussion, one must obtain a perspective on the total problem. There are many causes of upper airway obstruction: congenital defects such as choanal atresia and oral airway disorders, mass lesions whether neoplastic, infectious or foreign body, as well as conditions promoting edema or secretion can all induce obstruction to air movement. Vascular anomalies make

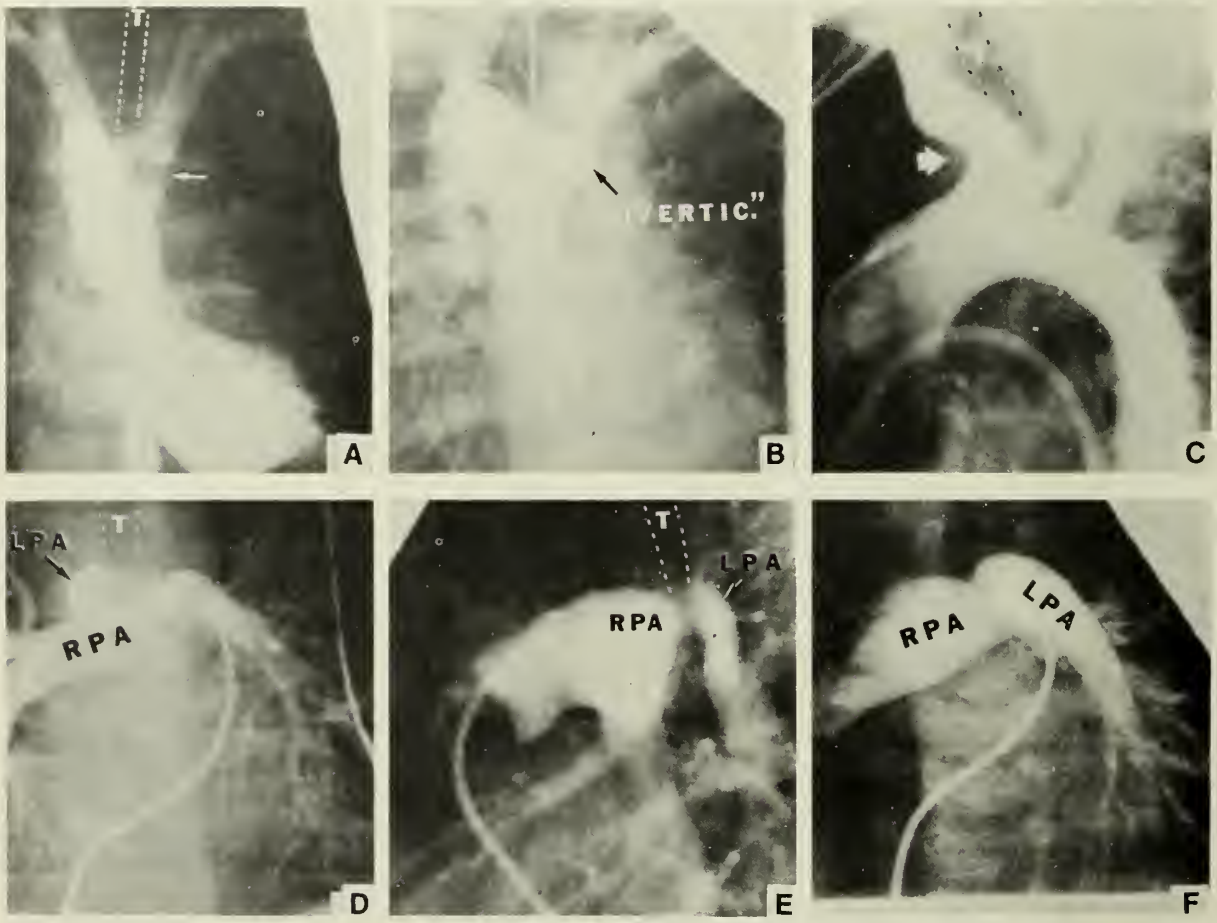

Figure 3.—Angiograms in vascular compression of the upper airway. **A,** Double aortic arch surrounding trachea (T); arrow indicates short atretic area in the ventral (left) aortic arch which can be severed surgically to disrupt the vascular ring. **B,** Oblique aortogram showing right aortic arch and diverticulum ("divertic") of Kommerell which is connected by the ligamentum arteriosum to the pulmonary artery thus completing the vascular ring. **C,** Lateral aortogram showing course of innominate artery—initially posterior (arrow) apparently compressing the trachea (T). **D,** Pulmonary arteriogram demonstrates origin of the left pulmonary artery (LPA) from the right pulmonary artery (RPA)—the pulmonary artery sling. **E,** Lateral view of pulmonary artery sling showing the trachea (T) encased by pulmonary arteries, the right (RPA) anteriorly and the left (LPA) posteriorly. **F,** Pulmonary arteriogram in patient with tetralogy of Fallot and absent pulmonary valve; there is massive dilatation of the right pulmonary artery (RPA) and moderate enlargement of the left branch (LPA).

up a small rare subgroup of conditions that produce airway obstruction.

There are three vascular structures that can compress the trachea or bronchus: the aorta, the pulmonary artery branches and the left atrium (Table 2).

The Aorta

There is a normal phase in the embryologic development of the aortic arch in which there are two aortas: ventral and dorsal. Usually, the dorsal aorta involutes leaving the ventral one to traverse the left mainstem bronchus, producing a left arch. Occasionally, only the dorsal aortic branch remains producing a right aortic arch.[11] Very rarely, both arches remain and fuse posteriorly to form the descending aorta. This condition—double aortic arch—always causes a vascular ring regardless of which side is dominant. While both branches around the trachea may be patent, it is possible to have a portion of one of the branches atretic (Figure 3A) with a fibrous cord connecting to the descending aorta and completing the vascular ring.[12]

It must be remembered that the ductus arteriosus or its descendant the ligamentum arteriosum essentially always lies to the left of the trachea. When the aortic arch is on the right and especially when part of the aorta is behind the esophagus, the components are present to form a vascular ring. The ring is formed by ascending and right-sided aorta, the retroesophageal aorta, the ligamentum arteriosum and the pulmonary artery. In many of these cases (Figure 3B) the retroesophageal aorta protrudes to the patient's left and has been called the diverticulum of Kommerell[8]; this structure is the landmark for the ductus arteriosus and is usually associated with a vascular ring.

An exceedingly rare condition has been described in which a vascular ring is formed by a left arch, retroesophageal aorta, and right-sided ductus arteriosus.[13] Review of published case reports suggests that this is either a complete mirror-image of the usual (right arch with left ligamentum) vascular ring or is a variant of double aortic arch with an atretic right (dorsal, anterior) limb.

Innominate Artery Syndrome

In the 1960's Berdon[5,14] and others wrote extensively about the "Innominate Artery Syndrome"; in this condition an aberrant course of the innominate artery is associated with anterior compression on the trachea and thus obstruction of the airway. Enjoying an immediate and enthusiastic vogue, the so-called innominate artery syndrome was extensively overdiagnosed and subsequently fell into disrepute. While the condition is clearly not as common as previously thought, it was diagnosed in three of our patients by angiography. In one child the condition was confirmed surgically, in one the symptomatology remained mild and no operation was carried out and the third patient (patient 7, Table 1) is worthy of detailed comment.

A 16-month-old infant with respiratory noises commencing at 3 weeks of age had four episodes of pulmonary infection within the first year of life. She slept in a supine position with her pillow behind her neck. Bronchoscopy carried out elsewhere suggested discrete anterior (but nonpulsatile) compression of the trachea. Aortic arch angiography (Figure 3C) showed an unusual course of the innominate artery from which also arose the left common carotid artery. *Innominate artery syndrome* was considered and the child was scheduled for arteriopexy. However, bronchoscopy was repeated preoperatively; a large segment of concentric stenosis of the lower trachea was found, shown by bronchography (Figure 1H). Thus, despite the apparent innominate artery syndrome, the patient's respiratory difficulties were intrinsic to the trachea rather than secondary to extrinsic (vascular) compression.

It is generally accepted that the thymus *never* causes compression of the upper airway. Our experience provided an exception to this dictum and emphasized the need to maintain a flexible attitude towards these patients. At operation in patient 8 (Table 1), an ectopic limb of the thymus was found behind the superior vena cava, connected to the main body of the thymus by a thick fibrous cord. Obstruction of the trachea was immediately relieved when the fibrous strand was severed.

Pulmonary Artery Branches

We now turn our attention from the aorta to the pulmonary artery (Table 2). When the left pulmonary artery arises from the right branch instead of the main trunk (Figure 3D) compression of either the trachea or the right mainstem bronchus can occur.[15,16] This is a condition in which, on a lateral x-ray of the chest, a mass is

seen *between* the trachea and esophagus (Figure 1E). A lateral angiogram (Figure 3E) dramatically shows how the trachea is narrowed posteriorly by the aberrant course of the left pulmonary artery coming from the right side. Note the tracheal air column "enveloped" by pulmonary arteries.

Tetralogy of Fallot with absent pulmonary valve syndrome is another rare cause of upper airway obstruction which we have seen recently. The unusual hemodynamics causes massive dilatation of the branch pulmonary artery,[17] usually the right (Figures 1D and 3F). Progressive enlargement and exaggerated pulsations of the pulmonary artery cause upper airway obstruction limited to the right side.

Left Atrium

In addition to the aorta and the pulmonary artery, the third vascular structure which can cause upper airway obstruction is the left atrium. Either left-to-right shunts or malfunction of the mitral valve can cause enlargement of the left atrium. Normally the left atrium is located just beneath the left mainstem bronchus; consequently dilatation of the left atrium presses up from below causing obstruction of the left bronchus and unilateral airway obstruction on the left.

Cardiac catheterization studies were done in each patient. Controversy does exist regarding the need for angiograms in all cases.[12] Techniques developed here[18] for aortic arch studies using the *venous* approach have stimulated angiographic studies because the dangers of retrograde arterial catheterization can usually be avoided. We feel strongly that no simple rule can be applied to all cases; individual determinations of proper diagnostic studies is the best approach.

Surgical Therapy

JOHN J. LAMBERTI, MD:* The surgical relief of upper airway obstruction caused by abnormalities of the aortic arch or its branches is generally straightforward. Before describing the surgical approach, I would like to comment on the diagnostic evaluation. Many surgeons believe that routine angiography or bronchoscopy is unnecessary in patients with an obvious vascular ring: stridor and roentgenographic evidence of tracheal compression in association with a diagnostic barium swallow are considered sufficient evidence for surgical therapy. Although angiography is of very little risk with present techniques, an aortogram is not required in all cases. In fact, in some instances, aortography may not clearly delineate the cause of airway narrowing. Nonetheless, angiography is indicated whenever the diagnosis is in question; oblique views may be helpful and several biplane angiograms may be necessary.

Bronchoscopy in infants—once a relatively high-risk procedure—has been well served by recent advances in technique, especially use of flexible fiberoptic bronchoscopes. When anomalous origin of the innominate artery is suspected as a cause of tracheal compression, bronchoscopic confirmation of a discrete anterior pulsatile tracheal compression is required before surgical intervention. However, in conditions such as double aortic arch, or right aortic arch with left ligamentum arteriosum, bronchoscopy is rarely indicated.

There have been relatively few innovations in the treatment of aortic arch anomalies since the first operation for this condition was described in 1945.[19] Double aortic arch or right aortic arch with aberrant left subclavian artery and vascular ring are all approached through a left thoracotomy which allows intraoperative delineation of the exact relationships. In 1953 Robert Gross summarized his experience with the surgical treatment of aortic arch anomalies[20] and, more than 25 years later, his recommendations continue to be valid. In cases of double aortic arch, the surgeon must divide the smaller or atretic aortic arch (usually the anterior one) in order to maintain adequate blood flow to the systemic circulation. The operation consists of division of the ligamentum arteriosum followed by division of the aortic arch at its narrowest point. Usually this will be between the left subclavian artery and the descending aorta. On occasion it may be technically easier and anatomically more appropriate to divide the arch between the left carotid and left subclavian artery. In such cases, the left subclavian artery becomes the distal-most branch of the right aortic arch system. In most cases, when the vascular ring is divided, immediate release of vascular compression is noted by the surgeon and the anesthesiologist may note that airway resistance has decreased. In cases of right aortic arch with aberrant origin of the left subclavian artery and left ligamentum arteriosum, there may be posterior compression of the esophagus as well

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as airway compression. Early descriptions of the surgical treatment of this entity indicated that the ligamentum arteriosum and the left subclavian artery should be divided. In such cases the vertebral artery should be ligated to prevent the subclavian steal syndrome. At the University of Chicago we reimplanted the left subclavian artery into the left carotid artery at the time of operation for this type of vascular ring on two occasions. This approach preserves blood flow to the left upper extremity as well as dividing the vascular ring and relieving posterior compression of the esophagus.

When the tracheal compression is caused by an anomalous innominate artery, the operation is best carried out by means of a median sternotomy or right lateral thoracotomy. The procedure involves anterior fixation of the innominate artery to the sternum. As previously indicated, innominate artery compression of the trachea is a rare cause of vascular compression and intraoperative bronchoscopy is an integral part of the therapy for this subset of patients.

Pulmonary artery sling has been surgically treated for many years and most early reports indicated satisfactory relief of tracheal compression. The left pulmonary artery is divided at its origin and transplanted to its normal location.[15] However, adequate long-term patency of the left pulmonary artery-to-main pulmonary artery anastomosis has been difficult to achieve.[16] This operation can be done through a left thoracotomy. We prefer a median sternotomy and utilization of cardiopulmonary bypass; additional suggestions include the use of microvascular techniques and the creation of a wide, spatulated anastomosis. In our patient, restudy a year after operation confirmed wide patency of the reconstructed left pulmonary artery and normal pulmonary arterial flow distribution shown by lung scan. It is important to emphasize that, in addition to secondary tracheomalacia, congenital tracheal abnormalities can occur in association with the compression caused by pulmonary artery sling[16]; circumferential narrow tracheal cartilages have also been reported.[21] In such patients, relief of the compression may not improve lower airway constriction and a procedure on the trachea itself may be necessary. Many advances have been made in tracheal surgical procedures and we now believe that the distal half of the trachea can be resected with excellent expectations of success. Serial bronchoscopic evaluation is an integral part of the overall care of these patients.

Tetralogy of Fallot with an absent pulmonary valve is a rare condition which is quite difficult to manage.[17] Patients presenting in infancy usually have symptoms of airway compression due to aneurysmal dilatation of the pulmonary arteries; severe hypoxemia is uncommon in these infants. Few surgeons have extensive experience with this lesion. It is the general consensus that the usual repair of tetralogy (closure of the ventricular septal detect and enlargement of the right ventricular outflow tract) is not adequate therapy for this lesion. As a minimum, a new pulmonary valve should be implanted and the surgeon should consider transplantation of the right pulmonary artery to a position anterior to the superior vena cava. The postoperative course tends to be complicated. The right mainstem bronchus may cause troublesome airway narrowing for months after the operation. In successful cases the bronchial narrowing has improved and eventually the children are weaned from the ventilator and discharged from hospital.

In the modern era it is most unusual to see a patient with such enlargement of the left atrium that left mainstem bronchus compression is noted. Treatment is directed at correction of the intracardiac defect producing left atrial enlargement. Results can be excellent. Recent improvements in the development of bioprosthetic heart valves may prove useful when valve implantation is required in infancy.

Summary

DR. WALDMAN: *In vascular compression of the upper airway in children, symptoms tend to start early and be variable; growth is usually normal. Multiple radiographic studies are available for evaluating the airway, including high kilovoltage films, barium swallow, computerized axial tomographic* (CAT) *scanning and bronchography. Impairment of the cough and other respiratory defense mechanisms leads to recurrent infection, respiratory failure, or stridor and wheezing. Compression of the upper airway can be caused by three vascular structures: the aorta or its main branches, the pulmonary artery branches and the left atrium. Surgical therapy is available for essentially all forms of vascular compression but must be based on a detailed understanding of the anatomy and pathophysiology. The diagnostic*

and therapeutic approach must be individually determined in every case.

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The RH Factor in Emergency Transfusions

WE NORMALLY GIVE Rh-positive people Rh-positive blood, but you can give Rh-negative blood; and in an Rh-negative recipient, you can give Rh-positive blood if it is really a life-threatening circumstance. In a woman who may become pregnant in the future, one would not like to immunize her to Rh. But when you have a ruptured aortic aneurysm in a 55-year-old man or woman and you only have two or three units of Rh-negative blood, the thing to do is switch. You really are not going to cause any problems to that patient. They may become immunized to Rh some months later and they may, if they get future transfusions, have to get Rh-negative blood; but when it comes to a question of lifesaving, we are not too hesitant about switching the Rh-negative patient to Rh-positive blood.

—HERBERT F. POLESKY, MD, *Minneapolis*

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Paroxysmal Nocturnal Hemoglobinuria—Present Status and Future Prospects

Tenth Annual Paul M. Aggeler Memorial Lecture

Given October 9, 1979

San Francisco General Hospital Medical Center

WENDELL F. ROSSE, MD, *Durham, North Carolina*

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

DR. WALLERSTEIN:* *This is the tenth year of our lectures in honor of the late Paul M. Aggeler, a man best known in science for his discovery of factor IX and for his work on qualitative platelet defects. But far more important, he is remembered as a friend, counselor and conscience for many of us. We established this lectureship to honor him as a teacher whose life touched us all in his respect for science, patients, colleagues and students. We have with us Wendell Rosse whose own career so well epitomizes this kind of clinical investigator.*

Wendell graduated from the University of Chicago School of Medicine, pursued his residency training at Duke University, and developed his scientific research skills at the National Cancer Institute and, later, with Dr. J. V. Dacie in London. Dr. Rosse is now Professor of Medicine at Duke and Chief of the Hematology and Oncology Division there. He has held many other prestigious lectureships (perhaps the best known is the Stratton Lecture of the American Society of Hematology in 1976) and has received many honors in American medicine. His areas of interest have been related primarily to red blood cells and their disorders—erythropoietin, complement, cold agglutinins and immune hemoglobinemias. He will discuss paroxysmal nocturnal hemoglobinuria—its present status and future prospects.

DR. ROSSE:† Although I did not know Dr. Aggeler, I and many hematologists of my generation were influenced by him, and others like him who espoused the philosophy that hematology offers an ideal setting in which to apply the burgeoning

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knowledge of the basic sciences to clinical problems. His untimely death cut short his own efflorescence, but what he built and what he stood for remains clearly evident. That, as Horace said, is "A monument more lasting than one of brass."

I shall discuss a complex and fascinating disease, paroxysmal nocturnal hemoglobinuria (PNH). This is an uncommon but not rare disease, and much of what I will discuss has evolved from cases of patients which I have followed. I have studied the blood of some 80 patients with PNH, 40 of whom I have managed clinically. Of these, I am currently following 20 cases on a regular basis in the clinic. Although this obviously represents a nonrandom sampling, it indicates that although PNH is not a public health menace, it remains an important disease.

Much of its importance arises, however, not from its prevalence but, rather, from what it is able to teach us about the physiology of the bone marrow and its products. It was once said that he who understood syphilis understood clinical medicine. Although I make no such grandiose claims for PNH, I will say that when we come to fully understand PNH, we will be much closer to understanding the control of proliferation of marrow cells, the cause of leukemia, the interaction of serum proteins (especially complement) with the cell membrane, and the structure of abnormal cell membranes. This will cut a wide swath across the spectrum of hematologic processes.

Paroxysmal nocturnal hemoglobinuria is misnamed and is usually misclassified. It is misnamed because the occurrence of hemoglobinuria at night is only one of the symptoms associated with PNH, and it is misclassified among the hemolytic anemias because the implications of this disease are much wider than the hemolysis. However, it is not unnatural that this should have happened because hemoglobinuria, when it occurs, is clearly the most dramatic symptom exhibited in patients with PNH. The condition was first described in 1866 by William Gull,[1] a physician at Guy's Hospital, London. In the charming, somewhat chatty manner of clinical reports of that era, he reported the case of a tanner who, remarkably, had "hematinuria" in variable degrees, although usually worse in the morning. Gull recognized that the pigment in the urine was not due to the presence of red blood cells. In the Remarks section of the case report, he described on a day-to-day basis the color of the patient's urine, a luxury that few editors of journals would permit today.

He described the color as going from indigo to mahogany to amber. This classification system is, I think, slightly inferior to one which was developed by a patient of mine who is a wine connoisseur. He described the color of urine as ranging from port through burgundy to claret to rosé and on to chablis. Nevertheless, we can see from Dr. Gull's description that his patient had paroxysms of dark urine, and that one of these episodes followed an infection of the lymph nodes, otherwise undefined. This exacerbation of hemoglobinuria following infections is typical of patients with PNH.

The next description of which we have a clear record was that of Paul Strübing,[2] an exceedingly observant German clinician from a small clinic in Griefswald. In 1882 he reported in the *Deutsche Medizinische Wochenschrift* a patient with paroxysmal hemoglobinuria which, like that in Gull's patient, was worse at night. In addition to a precise description of the clinical setting, Strübing made several fine clinical observations. He noted an exacerbation in response to exercise, as well as increased hemoglobinuria upon drinking beer, a symptom that I have not seen noted since. Perhaps the quantity of beer ingested by subsequent patients has not been sufficient to match that of Strübing's patient. Strübing hypothesized that the abnormality resided in the red blood cells; however, he thought that hemolysis occurred as these abnormal red blood cells circulated through the kidney. He gave his patient iron, which had become a common remedy in those days for any form of anemia, and noticed an exacerbation of hemoglobinuria. He correctly interpreted this on the basis of his theory that the condition was due to the production of new cells that were then hemolyzed. It has only been in recent years that this perspicacious observation and interpretation have been confirmed fully.

Subsequent to Strübing's report, several other descriptions of PNH have appeared. The most famous were those of Marchiafava[3] and Micheli.[4] Their fame rests not so much on any additional information imparted by their observations (in fact, the major contribution appears to be the description of "perpetual hemosiderinuria" by Marchiafava) but, rather, in the fact that their names were seized upon as eponyms—much of the European literature continues to use the name Marchiafava-Micheli syndrome for PNH. Because of the difficulties with the name that was finally adopted, perhaps an eponymous designation is

better. However, in this case it should be called, more correctly, the Gull-Strübing disease rather than the Marchiafava-Micheli syndrome.

The next significant observation was made by the Dutch physician Hijmans-van den Bergh, who is better known for his observations on the detection of bilirubin. In the *Revue de Medecine* (1911), he described a patient with paroxysmal hemoglobinuria in whom he followed up Strübing's suggestion that the red blood cells were abnormal. Thus, he incubated the patient's cells in the patient's own serum, as well as in ABO-compatible serum with and without carbonic acid. He discovered, to his amazement, that the patient's cells were hemolyzed, both in the patient's own serum and in the normal serum, when carbonic acid was present. This was the first acidified-serum lysis test.

In each of these descriptions, a different name was given to the syndrome, which essentially left it without a name. A disease with no name has no standing whatsoever, and it was only after several more clinical descriptions that the name *paroxysmal nocturnal hemoglobinuria* was given by Enneking.[6] As I will argue later, this is an incomplete and somewhat erroneous name, and yet it is by this name that the syndrome is known.

Our understanding and ability to diagnose PNH took a quantum leap forward with the studies in the late 1930's by Thomas Hale Ham.[7,8] In an article that ranks with that of Strübing as a classic in the field, Ham described the acidified-serum lysis test, often referred to as the Ham test in the United States. The test is exceedingly simple. Normal serum that is type compatible is acidified to a pH of 6.4. Under these conditions, PNH cells are hemolyzed, particularly if the serum is supplemented with magnesium. If the serum is heated to destroy complement, the lysis is not seen. Few normal cells or the cells of any other patients, with one minor exception, are lysed in this test. This test has become and remains, in usual clinical laboratories, the test that defines PNH.

Ham made the critical observation that the defect of the red blood cells in PNH consists of an unusual susceptibility to the hemolytic action of complement. We are still trying to answer the questions raised by these observations.

With the use of the acidified-serum lysis test to define patients who have PNH, it became clear that the clinical presentation may be quite different from that described by Strübing. In particular, many patients had abnormal cells as detected by this test, but did not have hemoglobinuria. In fact, some patients had few signs of overt hemolysis; others simply had chronic hemolytic anemia without overt hemoglobinuria; some patients had typical hemoglobinuria that was paroxysmal and nocturnal, and still others had severe hemoglobinuria in which it was often difficult to detect an exacerbation during the night. We now understand more about why such a wide variation in the amount of hemolysis should occur.

Dacie[9] had observed that when the cells that survived acidified-serum lysis were again treated with acidified serum, little or no more hemolysis occurred, and, yet, a proportion of the cells remained unlysed. This suggested that two populations of cells existed, one of which was normal. Red blood cell survival curves that were biphasic, showing a rapid diminution in survival followed by a more normal survival, also suggested the presence of two populations. Dacie and I[10] showed the existence of the two populations more directly in vitro in a series of experiments in which red blood cells from normal persons and PNH patients were hemolyzed by increasing amounts of complement in the presence of excess antibody. The tests indicated that normal cells were extremely resistant to the lytic action of complement in vitro by the fact that large quantities of complement were required for their lysis. In addition, they showed that normal cells consist of a single population by the fact that when the concentration of complement is plotted on a double logarithmic scale against a function of lysis (that is, the fraction lysed divided by the fraction unlysed), a straight line results. The lysis of PNH cells in a similar system disclosed two populations: one of which was virtually normal in its requirements of complement for lysis and the other of which required much less complement to bring about lysis. It is the presence of such a population of cells, which are more sensitive to lysis by complement, that characterizes PNH. A further advantage of using this technique to detect PNH cells is that the proportion of cells in the population may also be calculated.

Further studies disclosed that there were two kinds of complement-sensitive cells, one of which was intermediate in sensitivity between the originally described abnormal population and the normal cells.[11] These populations have been relabeled PNH I, PNH II and PNH III. PNH I designates the normal-appearing cells, PNH II the moderately abnormal cells, and PNH III the particularly abnormal cells (Figure 1). The most common com-

bination is PNH I and PNH III cells, occurring in approximately 80 percent of all patients. PNH II cells are irregularly present and are much less common. Some patients have only PNH I and PNH II cells and some have all three varieties of cells. A few patients have no detectable normal cells and, rarely, a patient has only PNH II cells (Table 1).

The proportion of abnormal cells varies greatly from patient to patient (Figure 2). Most patients with PNH III cells have them in relatively small proportions; however, the proportion of PNH II cells tends to be greater. The degree of hemolysis observed clinically is dependent on two factors: the proportion of abnormal cells and the degree of their abnormality. If few PNH III cells are present, little evidence of hemolysis will be seen. When the amount is between 20 percent and 50 percent, infrequent bouts of hemoglobinuria will usually occur. In patients with more than 50 per-

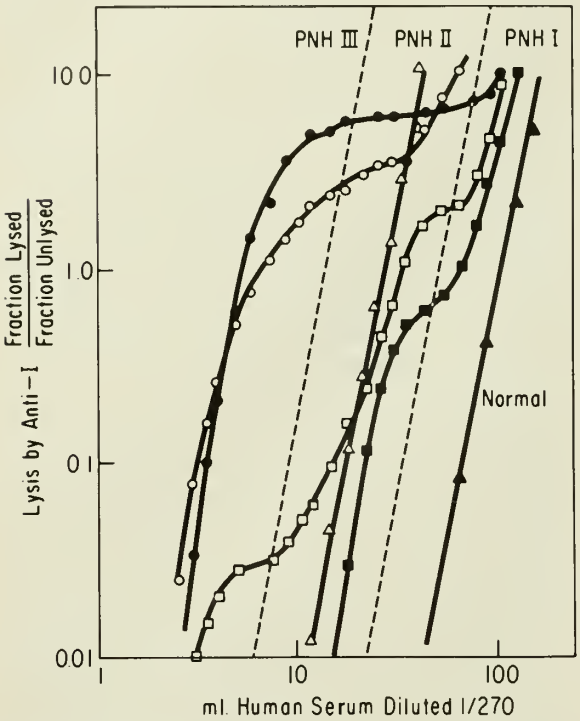

Figure 1.—Complement sensitivity curves of red blood cells of five patients with PNH and a normal control (solid triangles). Cells are sensitized with excess antibody (anti-I) and lysed with limiting amounts of complement as shown on the abscissa. The quotient of the fraction lysed divided by the fraction which is not lysed is shown on the ordinate. Three types of PNH cells are distinguished: PNH I cells which require about the same amount of complement for lysis as normal cells; PNH II cells, requiring somewhat less complement for lysis than normal cells, and PNH III cells which require very much less complement than normal cells for lysis. The presence of two populations in four of the five patients is shown by inflections in the curve; in one patient (shown in open triangles) and in the normal control, the presence of only one population of cells is indicated by the ortholinearity of the curve.

TABLE 1.—*Patients Grouped According to the Types of PNH Red Blood Cells in the Peripheral Blood**

Group	Type of PNH Cells Present I	II	III	Percent of Patients in Group
1	+	..	+	78
2	..	+	+	3
3	+	+	+	9
4	+	+	..	9
5	..	+	..	1

*Blood of 75 patients was examined.

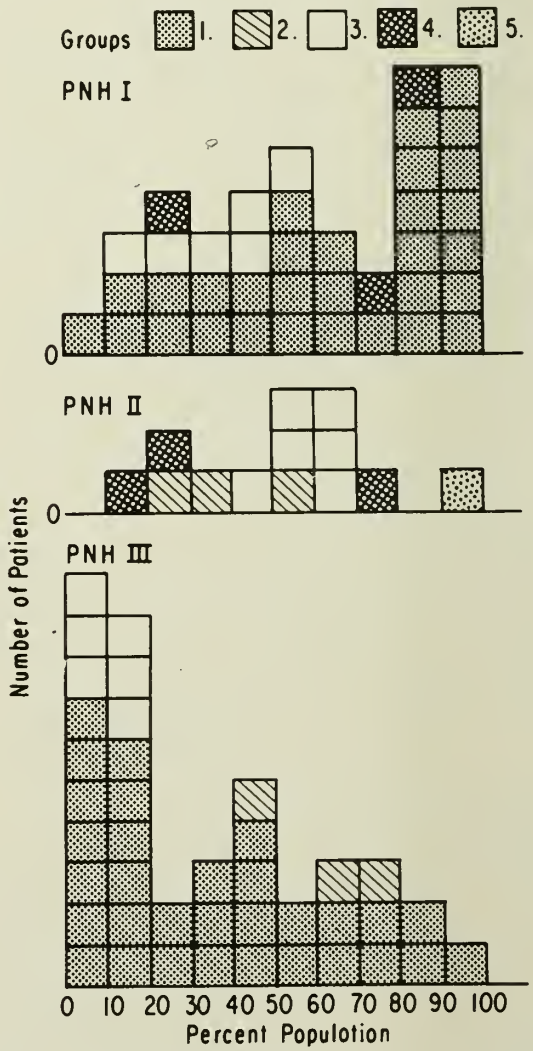

Figure 2.—The distribution of the size of the populations of red blood cells in 44 patients with PNH. The percent of the population in deciles is shown on the abscissa. Each square represents the population of a single patient. (Patient groups are given in Table 1.)

cent PNH III cells, hemoglobinuria will be fairly constant. However, patients with PNH II cells, even in large proportions, often have only intermittent hemoglobinuria. Hence, the variability of presentation can be explained by more detailed knowledge of the illness.

What causes this unusual sensitivity to activation by complement? We have spent considerable time trying to elucidate this question, which has required detailed study of the reactions of complement. Complement is a highly complex group of proteins that interact in a defined sequence to bring about the lysis of cells. It may be activated either by antibody in the classic pathway or by a number of reactions that activate the alternative pathway. Regardless of the pathway activated, PNH cells are more readily lysed. This suggests that the differences between PNH cells and normal cells should be found in the latter steps. We have found this to be the case. When the classic pathway is activated, PNH cells and normal cells fix the same amount of antibody, the same amount of C1, C2 and C4.[12] On the other hand, both PNH III and PNH II cells fix much more C3 than normal cells.[11,12] This is also strikingly true when the alternative pathway is activated: vastly more C3 is fixed to PNH cells than to normal cells. However, this cannot be the entire difference because the severely abnormal PNH III cells are more sensitive than the moderately abnormal PNH II cells.

The lysis by complement is brought about by the intercalation of a protein complex (C5-C9) into the lipid bilayer. This may be in the form of a doughnut, thus resulting in a water-soluble pore, or these components may act as detergent. Either way, free flow of ions occurs and the cell is no longer able to maintain the osmotic relationship between the inside and outside. As a result, a net influx of water occurs and the cell swells and lyses. This complex of protein is visible under an electron microscope as small hydrophilic areas by negative staining. Although many of these complexes are formed on the membrane, few of them are capable of penetrating through the membrane to effect lysis. By assessing carefully the number of such lesions and relating it to the degree of lysis, we have concluded that the number of such detectable lesions on the membrane needed to obtain lysis of PNH cells is about a tenth of that required for normal or PNH II cells.[13] Hence, there appear to be two defects in PNH cells: increase of fixation of C3 (and, perhaps, C5), which is present on both PNH I and PNH III cells, and increased penetrability of the membrane by the complement complex, which is true only for the severely abnormal PNH III cells (Table 2).

TABLE 2.—*Abnormal Reactions of Complement with the Three Kinds of PNH Red Blood Cells*

	PNH I	*PNH II*	*PNH III*
Increased uptake of C3 when complement is activated by the classic or alternative pathway ...	No	Yes	Yes
Increased efficiency of the terminal complex (C5-C9) in penetrating the membrane	No	No	Yes

By my description so far, PNH is not too badly misnamed, although it occurs as a presenting symptom in less than half of the patients. However, there are other clinical features that do not appear to be related to hemolysis at all. One of the most dreaded complications in PNH is the formation of clots in several unusual venous sites. Most commonly, this occurs insidiously in the hepatic veins resulting in a variant of the Budd-Chiari syndrome.[14] Clots in the cerebral veins have been noted. The splenic vein and, in two cases, the veins of the dermis have been involved, the latter resulting in unusual necrotic skin lesions.[15] These clotting events sometimes occur simultaneously with the hemolytic episodes, and it has been suggested that something is liberated by hemolysis that results in intravascular clotting.

It has been shown that the platelets in patients with PNH are abnormally sensitive to lysis by complement.[16] We undertook to determine whether the platelets in PNH have the same membrane abnormality as the red blood cells: for a given amount of the activation of complement, whether by the classic or by the alternative pathway, a greater amount of C3 was fixed to PNH platelets.[17] It has been shown that the fixation of C3 to rabbit platelets causes a release reaction as manifested by the release of serotonin. This is the first step to activation that results in a platelet clot. Normal human platelets did not undergo such a reaction. When we investigated the platelets in PNH, however, they appeared to behave like the rabbit platelets, releasing serotonin upon the fixation of C3. This suggests that the clotting abnormality in PNH may be due to an abnormality of platelets that results in serotonin release and clotting.

It is not clear whether the platelet life span in PNH is diminished; chromium 51 studies have not shown this.[18] However, having worked with plate-

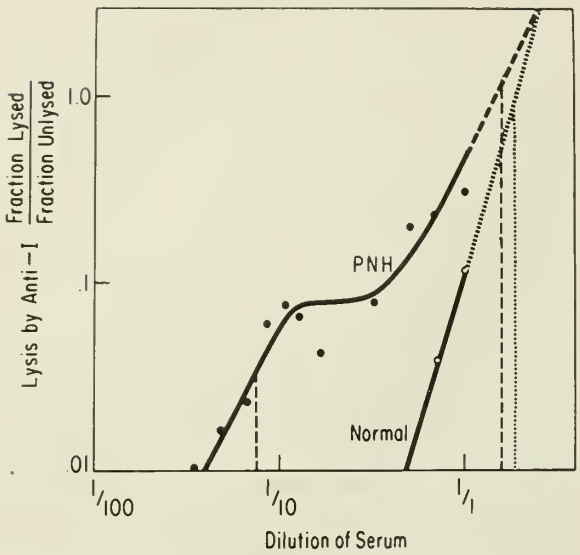

Figure 3.—Demonstration of two cell populations in the granulocytes of a patient with PNH. The test is essentially the same as for red blood cells (see Figure 1). Normal cells exhibit only one population whereas PNH granulocytes appear to be composed of two populations.

lets in vitro and having found them exceedingly difficult to handle, I am willing to consider that the abnormal population of platelets may have been altered during the radioisotope labeling such that the survival time of only the normal population was measured. Clearly, these studies need to be done more carefully. Many patients with PNH have thrombocytopenia, but it is not clear whether this is due to diminished survival, diminished production (see below), or both.

The granulocytes in patients with PNH are also abnormally sensitive to the lytic action of complement (Figure 3).[16] Again, there appear to be populations of cells that differ in their sensitivity.[19] As with the platelets and the red blood cells, the defect appears, at least, to consist of an excessive fixation of the third component of complement. However, the clinical manifestations of this abnormality in the granulocytes are not so apparent as for the other cells. It has been proposed that the cells in patients with PNH have a diminished response to chemotactic activities after exposure to activated complement.[20] These studies also need to be repeated. Granulocytopenia is not uncommon in patients with PNH,[21] but survival studies have given normal results.[22] Again, the possibility that only the normal cells survive the preparation and labeling procedures needs to be considered.

There are still some clinical features that are unexplained but very interesting. Most patients with PNH complain, on questioning, of esophageal tightness. It is particularly prevalent in the morning and during hemolytic episodes. We investigated this complaint in several patients and found it to be due to excessive strength of the muscular contraction. The esophageal peristaltic waves are generated normally, but have seven to ten times the force of normal esophageal waves when this symptom occurs. Thus, swallowing is painful and, on occasion, dangerous; one of our patients swallowed a potato chip without chewing it properly and a large esophageal ulcer developed.

Patients with PNH may also have severe abdominal pain; in two patients in my series it is the main clinical manifestation. This symptom sometimes is confused with an *acute abdomen,* which may result in an abdominal operation—a surgical procedure that is not without complications in patients with PNH. In one such patient, Blum and Gardner found an area of infarcted bowel,[23] and the infarction was thought to be due to venous thrombosis. Usually, however, the cause of the abdominal pain remains mysterious.

Patients with PNH may also have skeletal muscular pain, which may be acute, particularly when it occurs in the lower back. In such a case, it may require narcotics for relief. Recently, however, I have observed two patients who have had a syndrome of chronic muscular pain that occurred only after the diagnosis of PNH was made; a direct relationship was difficult to establish, and yet given the mysterious events that happen in PNH, it is entirely possible that the two syndromes are related.

It should be apparent by now why I believe that PNH is a misnomer. I think that it is misclassified because in almost all textbooks it is included among the hemolytic anemias. I grant that hemolytic anemia is its most obvious symptom; however, it is clear that PNH is much more than a hemolytic anemia, and that the defects are much more wide ranging than in the red blood cells alone.

It can be argued reasonably that PNH is the result of a disorder of the marrow stem cells. A stem cell may be totipotent (capable of producing B lymphocytes as well as the precursors of blood elements), pluripotent (capable of differentiating into any of the blood elements), or committed (sufficiently differentiated so that a single type of cell line can result). Recent studies have applied

the concept that the presence of a given abnormality in all three types of differentiated blood cells indicates that the abnormality exists in at least the pluripotent stem cell. Otherwise, a similar abnormality would have to be postulated as occurring somewhat independently in each of the differentiated cell lines. Similar membrane abnormalities resulting in irregular interactions with complement occur in all three types of differentiated blood cells. It is logical to conclude that the PNH lesion arises in at least a pluripotent stem cell. Both normal and abnormal cells occur simultaneously in most patients, suggesting that a clone of such abnormal stem cells originates from a single event because of some proliferative advantage. Recently, we confirmed the observation of others[24] concerning the clonal nature of abnormal cells in PNH. In a patient heterozygous for glucose-6-phosphate dehydrogenase (G6PD) isoenzymes, we found that the greatly abnormal PNH III cells were all of a single isoenzyme, whereas the PNH I cells contained both isoenzymes. This clone of abnormal cells may arise in an injured marrow of patients with aplastic anemia.[25,26] Its growth may be rapid or may occur over several months. Sometimes the number of abnormal PNH cells remains small and the clinical manifestations are largely those of the aplasia, whereas at other times in other patients the population of abnormal cells predominates with resultant hemolysis and more classic manifestations of PNH. Sometimes the preceding injury is recognized, but more often it is not. As just noted, sometimes only one or another of the marrow-derived blood elements is diminished; however, most patients with PNH have an element of hypoplasia at some point in the course of their disease.

A further clue to the classification of the syndrome is the finding that in a small proportion of patients (five percent to ten percent) acute leukemia eventually develops.[27-29] When this occurs, the abnormal PNH clone disappears. Usually, the condition is acute myeloblastic leukemia, although recently, a patient with PNH was found to have erythroleukemia.

The fact that all three cell lines are affected by the disorder and that the disease might result in leukemia caused Dameshek,[30] ten years ago, to classify PNH among the myeloproliferative disorders. However, there are several other facts that do not fit this classification. All the other diseases of the myeloproliferative syndrome manifest an uncontrolled overproduction of one or another of the cell lines. Although patients with PNH may show a reactive erythroid hyperplasia, this is under physiologic control and, in addition, is frequently less than one would expect for the degree of anemia. Furthermore, as noted previously, PNH frequently arises in patients with aplastic anemia, and elements of aplasia persist.

More recently, the myelodysplastic syndromes, another group of disorders of the bone marrow, have been proposed. Because some investigators believe that the term *myelodysplastic* has been presumed by the neurologists, the term *hematopoietic dysplasia* has been suggested instead. With the understanding that I am not discussing spina bifida, I prefer the term myelodysplastic syndromes.

These syndromes are, like the myeloproliferative syndromes, stem cell disorders. However, they are characterized by hypoproliferation, relative or absolute, of all three cell lines. They consist of abnormal cell products in all three cell lines as well, as one would expect from this kind of disorder. A further difference from the myeloproliferative syndromes has been elucidated recently using cell culture techniques. When bone marrow from patients with the recognized myeloproliferative syndromes are cultured in vitro, they often result in a larger number of colonies than normal.[31,32] In the case of polycythemia vera, the colonies may not require the large doses of erythropoietin that are usually necessary for differentiation of erythroid colonies in vitro. In patients with chronic myelogenous leukemia, large numbers of granulocytic colonies are seen in response to a colony-stimulating factor specific for this cell line. Technology for growing megakaryocytic cells in vitro is still too new to have been tested in patients with essential thrombocythemia. In contrast, the cells from the bone marrow of patients with myelodysplastic syndromes do not proliferate in vitro.[33] In this regard they resemble the cells in the bone marrow of patients with acute leukemia.[34] Finally, like the myeloproliferative syndromes, the myelodysplastic syndromes ultimately result in acute myelogenous leukemia.

Several syndromes have been placed in the category of myelodysplastic syndromes. I will not describe them here, but only mention them for discussion. One of the more common ones is the ill-defined and poorly named syndrome characterized by hypoproliferative bone marrow and abnormal cells that often results in acute leukemia. The French call it "refractory anemia with

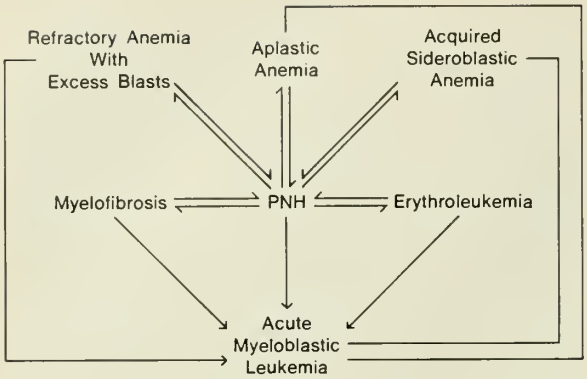

Figure 4.—Relationship of PNH to the other myelodysplastic syndromes. Clinical progression from one syndrome to another is indicated by the direction of the arrows.

excess blasts," but it is also called smouldering leukemia or preleukemia. Di Guglielmo syndrome, often called erythroleukemia, is also a myelodysplastic syndrome. In this disorder there is such dysplastic production of red blood cells that ineffective erythropoiesis is the major finding. Although in many of these patients acute leukemia develops promptly after the discovery of the di Guglielmo syndrome, in others it does not. Patients with acquired sideroblastic anemia may show the features of hematopoietic dysplasia. Although this syndrome is undoubtedly heterogeneous, at least a third of all patients with this syndrome, particularly those that show elements of hypoproliferation in all three cell lines, will eventually have acute leukemia.

Aplastic anemia is listed among the myelodysplastic syndromes. Again, this syndrome is undoubtedly due to heterogeneous causes, some of them thought to be immunologic. Nevertheless, there is also clear evidence that in some instances it is due to a disorder of the stem cell. Although the frequency of conversion to acute leukemia is low, it is well recognized. Finally, myelofibrosis has many of the elements of other myelodysplastic syndromes. In this case, however, some overlap with myeloproliferation is probable. The syndrome has been insufficiently studied to resolve the question.

I should like to concur with Sultan and coworkers[33] that PNH belongs among the myelodysplastic syndromes. It is clearly a stem cell disorder with abnormal products in all three cell lines, and is often characterized by hypoproliferation. We have recently confirmed that the bone marrow in patients with PNH does not proliferate in marrow culture despite the fact that the counts may be relatively normal and the bone marrow may have a normal appearance. Finally, as noted above, PNH results in acute leukemia.

The relationship of PNH to the dysplastic syndromes is further noted by the observed transitions from one to another (Figure 4). Most frequently, PNH emerges from aplastic anemia. On the other hand, patients with myelofibrosis, erythroleukemia, acquired sideroblastic anemia, and refractory anemia with excess blasts have all been shown to have PNH cells. The change is not always unidirectional. On rare occasions, patients with PNH may have the clinical syndrome of aplastic anemia, during which time the evidences of the abnormal population in the peripheral blood disappear. I have observed patients with PNH in whom acquired sideroblastic anemia, myelofibrosis and erythroleukemia develop. When this occurred, the PNH clone also disappeared. As pointed out earlier, all of these syndromes may result in acute leukemia.

Having described PNH in such careful detail, we ought to say something about its treatment. Obviously, the optimal treatment of the stem cell disorder is the replacement of the abnormal stem cell with a normal stem cell. To date, this is only possible with bone marrow transplantation. This has been tried in several patients with PNH, usually in those in whom primarily aplastic anemia is manifested.[35,36] In one interesting case, Thomas and associates[36] transplanted the bone marrow of a healthy identical twin to the other twin with PNH, using the syngenic marrow without previous preparation by radiation or chemotherapy. The PNH disappeared and the patient was cured. In other instances, the PNH cell population was obliterated by treatment before transplantation, and then after engraftment, the PNH was not seen. However, in one startling case, a patient with aplastic anemia who did not have PNH before transplantation was transplanted with presumably normal marrow and acquired PNH as soon as engraftment had occurred. Much remains to be learned about the transplantation of bone marrow in patients with PNH. Obviously, transplantation is not often possible, or even necessary, and patients need to be treated by other means.

Most patients with PNH become iron depleted because of the loss of iron in the urine. Therefore, some form of replacement therapy must be considered. Often, if iron is given at a time when the patient has a low hematocrit, a sudden burst

of hemoglobinuria may result. This was correctly attributed by Strübing to the advent of new cells; such a hemolytic episode can be prevented by either previous transfusion to suppress the wave of erythropoiesis that follows administration of iron to the iron-deficient patient or by the use of prednisone (see below), which suppresses hemolysis.[37]

In the mid 1960's Hartman and associates[38] found that in patients with PNH improvement often is seen after androgenic hormone therapy. The exact manner in which this is brought about is not clear—is it a result of additional stimulus to the dysplastic marrow to produce red blood cells or, as some suppose, is it a result of some effect on serum complement? In any event, at least 50 percent of patients have some improvement with androgenic hormones. At present, we are studying the use of some less androgenizing hormones to determine if certain unpleasant side effects may be avoided, particularly in women.

Prednisone can be effective in the treatment of PNH, but the doses required are often high.[39] I have employed a compromise in which the doses of prednisone are administered on alternate days. Of 16 patients treated, 12 have shown improvement on this regimen. No patient on this schedule has had serious clinical infections, whereas two patients who insisted on taking prednisone every day died of serious intercurrent infections.

With the use of these regimens it is usually possible to obtain at least a reasonable modus vivendi for PNH patients. However, if they fail, transfusion may be required. Although many patients can receive whole blood without incident, it is usually safer to transfuse washed or deglycerolized blood because of the occurrence of well-documented hemolytic episodes in which a patient's cells are hemolyzed after transfusion. This may result from the transfusion of small amounts of activated complement components in the plasma of unwashed blood.

Using these therapeutic regimens, it is often possible for patients with PNH to live a long time during which the PNH cell population can diminish substantially or disappear. While this process is usually very slow, it does offer the hope to PNH patients that they may be able to outlive the disease.[40] It would be a great step forward if other myelodysplastic diseases had a similar prognosis.

By exploring many of the subtle nuances of PNH, I hope that I have conveyed why I believe that this disease is misnamed and misclassified. However, I hope that you can also see how wondrous a disorder it is and how increased knowledge of the disorder may, in turn, help us immeasurably in better understanding the physiology of the bone marrow, the structure of the membrane, and the interaction of that membrane with complement. Clearly, it is the sort of challenge Paul Aggeler would have enjoyed.

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Street Drug Toxicology Laboratories

About kits to recognize street drugs: I do not recommend them at all, because when anyone takes the time to put together a kit, by the time they have completed it, the street drugs available in the area have changed significantly. So it would be meaningless. If you really want to do anything about street drugs, I would recommend that you go to the local hospital and convince the head of the pathology department to set up a street drug toxicology laboratory. You can have people anonymously send in samples and you can analyze them and find out what is actually present. You see what they look like and you get some idea of what's going on in your area. . . . By the way, if the people in your area tell you it is illegal: it is not. The Drug Enforcement Administration will give you a license to do it. If you are in a regular hospital, it is no problem at all. . . . I do not recommend you publicize in the newspaper what you find, . . . but you can disseminate the information to the medical community in your area—and that is more important than kits.

—SIDNEY H. SCHNOLL, MD, *Philadelphia*

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Important Advances in Clinical Medicine

Epitomes of Progress — Obstetrics and Gynecology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in obstetrics and gynecology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Constitutional Precocious Puberty

FEMALE PRECOCIOUS PUBERTY is defined as the initiation of breast development before the age of 8 years, or menarche before the age of 9 years. Precocious puberty is incomplete when only a single pubertal change occurs with no evidence of an effect of sex steroids elsewhere in the body. Precocious pubertal changes may be either isosexual, in which the secondary sex characteristics are in agreement with the organic determinants of sex, or may be heterosexual, in which the secondary sex characteristics are in disagreement with the organic determinants of sex. Isosexual precocious puberty may be related to causes outside of the central nervous system, referred to as pseudoisosexual precocious puberty or to causes within the central nervous system referred to as true isosexual precocious puberty.

The most common cause of precocious pubertal development is constitutional precocious puberty, a form of true isosexual precocious puberty. This disease is characterized by the premature attainment of adult function of the hypothalamic-pituitary-ovarian axis with the cyclic release of gonadotropins leading to adult levels of endogenous estrogen which in turn produces isosexual pubertal changes which may progress to menstruation and even ovulatory menstrual cycles. The cause of constitutional precocious puberty is not known. Symptoms may appear at any age, but are rare in the first year of life. The progression of symptoms may be rapid or slow, and rare spontaneous remissions have been reported. Under the influence of estrogen, growth is accelerated initially and the patients for a time are taller than their peers; however, the acceleration of linear height is quickly terminated as the distal epiphyses fuse prematurely and the patients' final height is less than their peers. The disease is not a detriment to the patients' general health but is the source of considerable emotional unrest, for both patients and their families. The most important long-term sequelae is the short stature.

Constitutional precocious puberty is a diagnosis arrived at by exclusion. Heterosexual causes of precocious puberty may be excluded by clinical observation. Incomplete forms of precocious puberty may be eliminated by the appearance of more than one pubertal change or the rapid advancement of height either recorded on a growth chart or the pronounced advancement of bone age compared with chronological age. Causes of pseudoisosexual precocious puberty are associated with prepubertal levels of gonadotropins and causes of true isosexual precocious puberty with adult levels of gonadotropins. When organic brain disease is

precluded by a normal neurological examination, the only diagnosis remaining is constitutional precocious puberty.

The treatment of this disease is less than satisfactory. There is no agent available that prevents the premature closure of the distal epiphyses. Medroxyprogesterone acetate inhibits ovulation, usually prevents menstruation and may cause some regression of the secondary sex characteristics.

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Ectopic Pregnancy: Current Etiology

THE NUMBER OF MATERNAL DEATHS due to ectopic pregnancies has decreased in the last 20 years, but there has been a far greater decline in maternal deaths from abortions. As a result, ectopic pregnancy is the leading cause of maternal mortality in the first trimester of pregnancy. Reviews indicate that a significant percentage of these deaths are preventable. A half to two thirds of all women with surgically proved ectopic pregnancies are seen in a medical facility more than 24 hours before admission for surgical operation.

Pelvic inflammatory disease and pelvic surgical procedures have long been suggested as etiologic factors in ectopic pregnancy. More recently it has been noted that pregnancies following tubal surgical procedures for infertility or tubal sterilization operations, and unwanted pregnancies which occur while women are using intrauterine devices (IUD's) or progesterone-only oral contraceptives are more likely to be ectopic. Conservative infertility operations to restore tubal patency result in an increased proportion of tubal pregnancies particularly with surgical procedures involving the distal portion of the tube. Ectopic pregnancy has been reported following both tubal ligation and tubal fulguration sterilization procedures. A previous history of tubal occlusion for sterilization does not exclude the possibility of ectopic gestation, and as these procedures are more frequently selected by family planning acceptors they will play an increasing role in the cause of ectopic pregnancy. Users of intrauterine devices have protection against both intrauterine pregnancies, and tubal pregnancies but the IUD is more effective in preventing intrauterine pregnancies than extrauterine gestations. Therefore, an unwanted pregnancy in an IUD user is more likely to be an ectopic gestation than is a pregnancy in women using barrier methods of contraception or no method of contraception at all. Progesterone-only oral contraceptives are associated with a 2 percent to 8 percent failure rate and the ratio of extrauterine to intrauterine gestations is increased compared with a population of noncontraceptive users.

A past history of pelvic operation either to restore tubal patency or to produce tubal occlusion and a contraceptive history indicating the present use of an IUD or the progesterone-only oral contraceptives increase the likelihood that a pregnancy will be an extrauterine gestation.

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Ambulatory Gynecologic Operations

AMBULATORY OPERATIONS, meaning any surgical procedure done without an overnight hospital stay, are now firmly established as a safe, economical and reimbursable mode of surgical practice. It is estimated that from 30 percent to 40 percent of gynecological operations that have traditionally been carried out with admission to hospital could now be done in suitable *come-and-go* facilities, with excellent care, and with significant savings in physician time and patient costs.

Suitable facilities for ambulatory gynecologic surgical operations are of three basic types: The hospital *come-and-go,* the freestanding surgical center and the office-based surgical suite. The hospital based *come-and-go* surgery has the advantage of immediate hospital backup in case of unanticipated need; established standards are easier to monitor but savings tend to be less. Freestanding surgical centers generally maintain high quality standards of care, general anesthesia capability and overall costs which are lower than hospital-based centers. The office-based surgical suite has the greatest potential for cost effectiveness, but also the furthest to go in establishing and monitoring quality standards of care. In general, operations that can be carried out with local anesthesia, such as dilation and curettage, are appropriate for an office-based surgical suite. Operations for which general anesthesia is preferred, such as laparoscopy and minilapa-

rotomy, are most commonly done in a hospital-based or a freestanding facility.

More ambulatory surgical facilities should be developed and used, whenever appropriate, for other surgical specialties as well as gynecology. When this trend toward most cost-effective surgical care reaches its full potential, it will have a major impact in lowering the overall cost of surgical health care, while preserving its high quality.

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The Use of β-Sympathomimetic Drugs for the Inhibition of Premature Labor

ALMOST ALL ORGANS including the uterus have α and β receptors. Stimulation of α receptors causes excitation, while stimulation of the β receptors causes relaxation. The β receptors have been subdivided into β_1 and β_2 receptors: The former are confined to the heart, while the latter are present in the vascular smooth muscle, myometium and bronchial tree.

Stimulation of β-adrenergic receptors has in recent years become the preferred method to inhibit uterine contractions in premature labor. Pharmacologic agents such as isoxsuprine, ritodrine and terbutaline have been employed clinically and with better success rates than achieved with use of alcohol or sedation.

The maternal cardiovascular side effects of β-sympathomimetic drugs include maternal tachycardia, palpitations, increased cardiac output and hypotension. These side effects vary from one agent to another depending on the degree of β_1 receptor stimulation. Whereas, isoxsuprine stimulates the β_1 and β_2 receptors, the other agents have β_2 selectivity. The maternal metabolic side effects are primarily due to muscle glycogenolysis and lipolysis, and include hyperglycemia, lacticidemia, hyperlipemia, hyperkalemia and increased oxygen consumption. Acid-base balance changes indicate acute metabolic acidosis. Compensatory mechanisms come into force after one to six hours of β-sympathomimetic infusions and the above metabolic changes return toward control levels. β-Sympathomimetic drugs cross the placenta and reach the fetus. There is an increase in fetal heart rate and serum glucose, but no change in the mean arterial pressure and acid-base balance when labor-inhibiting doses are used.

Baumgarten suggested the following treatment plan: immediate bed rest, sedation if the patient is very anxious and intravenous infusion of β-sympathomimetic drugs. A low dose schedule is initiated, and the infusion rate is increased every 15 minutes until uterine contractions stop. The labor-blocking dose is maintained for 24 hours, then gradually diminished to the minimum effective dose, which is maintained for another 24 hours. If effective, the intravenous infusion is stopped in 48 hours. Oral administration of the β-sympathomimetics is started in the hospital and continued at home until fetal maturity. The prophylactic use of β-sympathomimetics in patients at risk of premature labor has not been proved.

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Hysteroscopy

MOST HYSTEROSCOPIES may be carried out on an outpatient basis utilizing intravenous meperidine sedation and paracervical block anesthesia. The hysteroscopy should be scheduled in the early follicular phase. Hyskon Hysteroscopy Fluid, a 32 percent solution of dextran with an average molecular weight of 70,000, is not miscible with blood and therefore is the medium of choice.

Hysteroscopy is indicated in patients who have recurrent abnormal uterine bleeding. More than a third of these patients have a submucous myoma or endometrial polyp (or polyps) which may be missed even by the most thorough curettage. These may be resected or removed during hysteroscopy.

Hysteroscopy is indicated in women in whom an intrauterine device (IUD) is palpable within the cavity but cannot be removed and for those in whom the device cannot be felt but is shown (for example, by hysterosalpingogram) to be partially within the uterus.

The major application is in the diagnosis and treatment of intrauterine adhesions. Under direct visualization, the extent, density and location of the adhesions may be determined. Lysis of adhesions under direct vision is easy and safe, complete dissection is assured and normal endometrium is not traumatized. Following dissection of the adhesions, an IUD is placed and high dose estrogen therapy is used for two months.

Because endometrial carcinoma is considered both an indication (for accurate staging) and a

contraindication (possible tumor spread), the final role of hysteroscopy is uncertain. At present few data are available to strongly suggest an important role for hysteroscopy in patients with repeated abortions, congenital anomalies and unexplained infertility.

Contraindications are active uterine bleeding, recent uterine perforation or infection, and pregnancy. Complications (which occurred only rarely among 600 patients) include bleeding, infection, uterine perforation, and reaction to either the anesthestic or the medium used.

In summary, hysteroscopy is an extremely valuable technique for gynecologists. Although the indications are few, this technique greatly enhances our ability to care for patients with the conditions discussed. It is likely that future advances in hysteroscopy will lead to its even wider application.

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The Role of Bromocriptine in Gynecologic Practice

THREE RECENTLY DEVELOPED diagnostic techniques, a radioimmunoassay for prolactin (PRL), hypocycloidal polytomography of the sella turcica and computerized axial tomography (CAT scans), together with the release of the ergot alkaloid 2-Br-α-ergocryptine have signaled the arrival of a new era in medicine. We are now able to *diagnose* and to *treat* ailments which were barely understood at the beginning of the last decade.

It appears that the prevalence of galactorrhea, of pituitary adenomas and of menstrual abnormalities has increased. However, since more sensitive diagnostic techniques are available, we may be searching for these problems more carefully and the increased incidence may only be apparent. Many patients who have galactorrhea and most of those who have pituitary adenoma have hyperprolactinemia.

The use of bromocriptine has been approved only for women who have amenorrhea, galactorrhea and hyperprolectinemia but in whom there is no evidence of a pituitary tumor. A careful investigation is mandatory to select candidates for treatment. Galactorrhea is any unilateral or bilateral breast discharge which is neither purulent nor hemorrhagic in a patient who has not breast-fed nor been pregnant within the preceding 12 months. The presence of fat globules in the secretions confirms the milky nature of the discharge.

All patients with inappropriate lactation should have a serum thyroid stimulating hormone (TSH) determination in addition to a measurement of the PRL concentration. Primary hypothyroidism has been associated with amenorrhea, galactorrhea and hyperprolactinemia. If the TSH level is elevated, thyroid replacement therapy should be instituted. Radiographs of the sella turcica should also be obtained—initially cone views, but if these show no abnormalities, polytomography should be carried out. CAT scans are indicated in women with hyperprolactinemia to rule out a suprasellar mass which may be present even if the sellar architecture remains intact.

Women with hyperprolactinemia usually have oligomenorrhea or amenorrhea because of reduced pituitary FSH and luteinizing hormone production. This reduction then leads to anovulation and menstrual abnormalities. Bromocriptine reverses this defect by a dual action. This dopamine receptor agonist stimulates the release of prolactin-inhibiting factor via hypothalamic centers and also directly inhibits the release of prolactin by the pituitary gland. Serum PRL levels return to normal and thus the inhibition of cyclic pituitary and ovarian function is removed.

Treatment should be started with one 2.5 mg tablet per day to be taken with a meal (to reduce the chance and the severity of nausea). Within four to seven days the dose is doubled and this increase maintained. After four weeks the patient should be reexamined and another serum prolactin level obtained. If the serum PRL level or the amount of galactorrhea (or both) is unchanged, a third tablet should be added. This is the maximum dose. Approximately 80 percent of patients who are treated with bromocriptine respond with a return of serum PRL levels to normal (usually within one to two weeks), the resumption of ovulatory menstrual cycles (usually in four to six weeks) and the cessation of lactation (eight to ten weeks).

Although more than 800 pregnancies secondary to bromocriptine treatment have been reported with no increase in the frequency of congenital anomalies or multiple gestations, this agent may not yet be used for the management of infertility. (It should be remembered that data on more than 2,000 pregnancies had been reviewed before the release of clomiphene.) Therefore, a mechanical

method of contraception should be utilized during treatment. Therapy should be continued until a remission has occurred for a maximum of six months. Unfortunately, after stopping therapy with bromocriptine most patients have a recurrence of symptoms.

Side effects include nausea (usually transient) and vomiting in some patients. A variety of other gastrointestinal side effects as well as headaches, dizziness, lightheadedness and nasal congestion have been reported occasionally.

In the future, bromocriptine may be used for many indications. Of paramount interest will be its use in treatment of infertility, suppression of postpartum lactation and therapy for patients who have prolactin-secreting pituitary tumors. Other uses may be amenorrhea-galactorrhea without hyperprolactinemia, luteal phase defects, acromegaly, Parkinson disease, and some cases of breast carcinoma. Early reports of its use for men with hypogonadotropic hypogonadism have also been favorable.

In summary, the availability of bromocriptine has opened new vistas. This agent appears to be highly effective in therapy for patients with a wide variety of conditions. Factors limiting its widespread application in the immediate future are the occasionally catastrophic complications of pregnancy in a patient with a pituitary tumor and a still unproved freedom from teratogenic effects.

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The Pap Test: How Often?

CARCINOMA OF THE CERVIX ranks as the second most common gynecologic malignant condition with 20,000 new cases and 7,400 deaths reported in 1978. A preponderance of evidence indicates a continuum from dysplasia through carcinoma in situ (CIS) to invasive cancer. Although some precursor lesions may remain stable for years, or even regress, most are thought to progress over a variable period of time. On this basis it is logical to diagnose the dysplasias and CIS as early as possible because the therapy of cervical intraepithelial neoplasia (CIN) is relatively simple and complication-free compared with the therapy of invasive cervical carcinoma, and can allow preservation of reproductive function. These considerations are of even greater importance as the incidence of CIN lesions has reached epidemic proportions in the younger, sexually-active population. It has been estimated that more than 40,000 cases of cervical carcinoma in situ were detected in 1976; the annual rate appears to have increased since that report.

Although the cytologic smear represents a proven technique for the detection of precursor cervical lesions, recent information, such as in the Walton Report, has suggested that a yearly Papanicolaou (Pap) test is not cost-effective and is unnecessary for most women. However, this contention should not be accepted without qualification. A more logical approach would be to take into consideration the relative risk for a given patient population. A low-risk group would include women with a history of three serially normal annual Pap tests and an historical sexual pattern which includes an active coital life commencing after age 18, and involving few sexual partners. The conditions of these persons may safely be followed by cytologic sampling every two to three years. However, a high-risk group may be identified by the following: (1) a history of first coitus or pregnancy at an early age (<18 years) and (2) multiple sexual partners or prior diagnosis by an abnormal Pap test result. Additional high-risk factors include a history of herpes virus infection and sexual partners (1) previously married to a woman with cervical carcinoma or (2) with a history of penile or prostatic carcinoma. Women in this category should undergo cytologic cervical evaluation once a year or every six months.

The case for yearly Pap tests is emphasized by a report from Fox. In a group of 547 women with abnormal Pap test results, 195 (35 percent) had a history of previous negative cytology, and 41 (7.5 percent) had three prior negative smears. In 141 women (26 percent) cytologic atypia developed in less than two years from the last normal smear. Of great significance is that in 51 of 140 women (36 percent) significant atypia developed within six months of a negative smear.

In addition, a Pap test is the single most powerful stimulus that brings women to physicians' offices for annual examinations. Carcinoma of the breast represents the greatest cause of death from cancer in women, colorectal carcinoma is third and ovarian cancer is the most frequent cause of death from gynecologic malignancy. The

potential benefits of a yearly physical examination are obvious.

Until a technique of greater accuracy and logistic simplicity becomes available, annual Pap tests should be recommended in all but clearly low-risk women.

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Use of Glucocorticoids in Promoting Fetal Lung Maturation

DESPITE SIGNIFICANT ADVANCES in neonatal intensive care, the respiratory distress syndrome (RDS) in prematurely delivered infants is still associated with a high degree of morbidity and mortality. In an attempt to reduce the incidence and severity of RDS, the maternal administration of glucocorticoids 24 to 48 hours before the delivery of a premature infant has become part of our medical armamentarium.

The fetal lung is reported to be rich in glucocorticoid receptors. Glucocorticoids apparently cause cytodifferentiation of type II pneumocytes and stimulate the production and release of surfactant by induction of the enzyme phosphoryl choline transferase. The end point being an increase in the lecithin:sphingomyelin (L:S) ratio indicating pulmonic maturity.

The original indication for the use of glucocorticoids was in a patient in premature labor, with intact membranes. This indication has been broadened to include those patients with ruptured membranes and without evidence of infection. Most studies have failed to show any statistically significant increase in maternal or neonatal infections with the use of glucocorticoids in patients with premature rupture of membranes.

Obstetricians have been cautioned against the use of glucocorticoids to promote pulmonic maturity in pregnant women with severe hypertension because of a reported increase in antepartum fetal deaths. Steroid induced compromise of an already compromised placenta is the purported mechanism of action. However, others have shown that under controlled conditions, glucocorticoid therapy need not be an absolute contraindication in the hypertensive pregnant patient.

Concern has also been expressed as to whether the use of glucocorticoids could adversely affect the developing fetus or neonate. Studies in animals have shown an inhibition in growth and brain development; a reduction in the absolute number of circulating B and T cells, as well as neonatal adrenal insufficiency. Again, evidence for these comes mostly from studies in animals.

Whether betamethasone or dexamethasone is used is not important except perhaps that the latter has been reported to have increased binding to fetal lung receptors. What is important is that glucocorticoids have been shown to be effective in accelerating pulmonary maturity only in infants born at or before 32 weeks of gestation. The use of steroids after 32 weeks has not influenced the L:S ratio. Also, glucocorticoid therapy offers no protection when given less than 24 hours before delivery.

The role of glucocorticoids in accelerating lung maturity has been firmly established. However, what remains to be determined is whether the potential risks outweigh the intended benefit. Steroid therapy requires care and discretion and should be accompanied by adequate follow-up to study any possible adverse effects.

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A Second-Look Operation in the Management of Patients With Carcinoma of the Ovary

MUCH OF THE CONFUSION caused by the concept of a second-look laparotomy relates to the lack of a consistent definition. Second operations in patients with ovarian carcinoma are frequent and usually are related to therapy. These include, for example, surgical relief of intestinal obstruction as well as second attempts at tumor reduction. The term second-look laparotomy, however, should be reserved for those instances in which the procedure is carried out on a patient undergoing chemotherapy who appears clinically to be free of disease. The purpose of the operation is to document the patient's disease-free status, so that chemotherapy can be discontinued. The reported increased incidence of acute nonlymphocytic leukemia in patients on prolonged alkylating-agent therapy has precipitated interest in this procedure.

The second-look operation is far from a simple

procedure. If one chooses to do a laparoscopy, it should be understood that it is frequently followed by a formal laparotomy. If gross residual disease is present, which is not considered resectable, biopsy specimens should be obtained and laparotomy may be deferred. If, however, visualization is inadequate to make such a decision, or no disease is seen, it is mandatory to proceed with abdominal exploration. If resectable disease is present, it should be removed. If no gross disease is present, a thorough, complete and systematic exploration of the abdomen should be carried out. This should include washings of the pelvis and colic gutters for cytologic examination. Strand-like adhesions should be excised and sent for pathologic review. Biopsy specimens of the infundibulopelvic ligament stumps should be obtained. Random biopsies of the pelvic peritoneum are also suggested. If the uterus, tubes, ovaries or omentum are present, they should be removed. The retroperitoneal space is to be opened and the periaortic nodes sampled. Diaphragmatic biopsies are also of importance. It is imperative that this procedure be carried out through an incision which allows total visualization of the intra-abdominal contents. Only after such an operative procedure has failed to show residual carcinoma can chemotherapy be discontinued with confidence.

The largest reported series on this subject comes from the M. D. Anderson Hospital in Houston. Of 103 patients in whom second-look procedures were done, 23 patients were found to have no evidence of carcinoma. Of these patients, 19 remain clinically free of disease and are not receiving chemotherapy. In four who were free of cancer at the second-look operation, recurrent disease developed after therapy was discontinued. All had received only four courses of chemotherapy and the possibility of adequate sampling at the time of laparotomy was raised. Of the remaining 80 patients with tumor present at laparotomy, there was complete removal of all tumor in 29. Of these 29, 14 are living without evidence of disease, 7 are alive with cancer and 8 are dead of disease.

The use of second-look laparotomy in patients with ovarian carcinoma has the advantage of identifying those patients in whom chemotherapy can be successfully discontinued as well as the subgroup of patients who can be rendered disease free by surgical resection. The latter group may indeed benefit by the more aggressive chemotherapeutic regimens now being developed.

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Microsurgery in Gynecology

OCCLUSION OF THE FALLOPIAN TUBES accounts for approximately 20 percent of the causes of infertility. The occlusion may have resulted from infection with associated damage to the endosalpinx, or from a sterilization procedure. Tubes can be repaired surgically and, until recently, the instruments and sutures were the same as those used for most gynecological operations. The types of tubal surgical procedures done consist of (1) reimplantation of a tube occluded at the cornual end, (2) reanastomosis of separated portions of tube, (3) salpingostomy and (4) separation of peritubal and fimbrial adhesions.

Microsurgery, which has been used in other surgical specialties for several years, was brought into the gynecologist's armamentarium by Kurt Swolin, who published the first series of tubal repairs by this technique in 1967. The advantage of microsurgery is that it permits the use of small needles and fine sutures ranging from 5-0 to 10-0 in size. In order to use these materials an operating microscope with magnifications of ×5 to ×20, or loupe with magnifications of ×2.5 to ×6, is necessary. By using these instruments a gynecologist can reanastomose two separate ends of a fallopian tube in two layers, with a few fine sutures through the muscle layer and slightly thicker ones through the serosa. Bleeding is controlled by a bipolar cautery with a fine needle tip.

Tubes with the endosalpinx damaged by infection will continue to respond poorly to surgical therapy. Tubes which have had a segment removed for the purpose of sterilization, leaving two healthy portions, are ideal for repair. In these cases, two-layered reanastomosis can be obtained by microsurgery. Successful reanastomosis as shown by a subsequent pregnancy will depend on the skill of the operator, and should be at least 40 percent.

An important point in the workup before operation is to ensure that the couple does not have an additional cause for infertility, such as oligo-

spermia, failure to ovulate or hostile cervical mucus. An infertility workup should always be carried out, and maximum information obtained concerning the tubes by seeing the old operative records, using hysterosalpingography and viewing the tubes through a laparoscope. For couples where the only problem consists of tubal occlusion, microsurgery has improved the prognosis and enabled many previously infertile couples to achieve a pregnancy.

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Real-Time Ultrasound in Obstetrics

THE ABILITY to visualize and measure intrauterine structures has resulted in new information in the clinical practice of obstetrics. Real-time (RT) imaging is the term applied to ultrasound scanners that display moving structures. This is accomplished by high-speed presentation of a series of images at frame rates in excess of 30 per second, the usual level for flicker-free viewing. Image resolution has been greatly improved, although it is generally inferior to static B-scans.

The enthusiasm among physicians in RT echography is enhanced by the small size and ease of operation of this equipment, and the low cost and the short time involved in scanning the gravid uterus. Most units are portable and can be used at the bedside or in the office. Fetal movements and cardiac pulsation can be visualized from as early as eight weeks gestation, thus allowing differential diagnosis between threatened abortion and fetal demise. For amniocentesis, pockets of amniotic fluid can be identified and the depth for puncture be determined in order to avoid injury to the fetus, umbilical cord or placenta. In patients with third trimester bleeding the placenta can be localized.

The most useful measurement in evaluating fetal age and growth is the biparietal diameter of the skull. The accuracy of these measurements is approximately 2 mm with the use of RT as compared to caliper measurements of neonates delivered by repeat cesarean section. Sonar dating is indicated in patients with uncertain dates or size-date discrepancies, and in high-risk pregnancies where preterm delivery is likely if trouble arises later. The optimal time for dating is from 22 to 26 weeks because body size of all fetuses is rather similar during this period of pregnancy.

Optional equipment improving the efficiency of RT scanners is a camera to take pictures of representative tomograms, electronic calipers, a freeze-frame for measurements, and a key board for patient identification and labeling of structures on the scan.

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EDITORIALS

Some Thoughts on the Competence and Performance of Physicians

OF LATE there has been increasing interest in the competence of physicians and in how competently they actually perform in their practice situations. This interest has been within the medical profession and also in the public domain. It has been stimulated by the tremendous growth in medical knowledge, and the need to assure patients, the profession and the public that physicians are in fact keeping up with this progress. This has led to much attention being given to just what are the components of competence for a physician in practice, how can competence and performance in practice be measured by the physician or anyone else, and what part does informal, formal or mandated continuing medical education play in all of this. The answers are not nearly as simple as the uninitiated might think. The discussions at a recent two-day meeting of the Alliance for Continuing Medical Education (ACME) probed some of the questions and gave rise to some of the thoughts presented here.

• *How do practicing physicians learn or keep up?* It is suggested that physicians learn from their own practice experience, from professional peers and from academia. Learning from practice experience accumulates during a lifetime of practice and forms a personal data base of clinical experience. Learning from peers is generally unstructured and usually occurs around problems in patient care. Knowledge derived from academia is acquired in concentrated fashion during formal undergraduate and specialty training, and then becomes outdated unless steps are taken to prevent this from happening by means of formal or informal continuing medical education. It is probable that formal CME plays a relatively minor role compared with informal or self-directed physician learning.

• *Who is responsible that a physician remains competent and performs competently?* It turns out that this can only be the individual physician, and that this responsibility is to self, to patients, to the profession and to the public, which grants a license to practice on the basis of presumed competence. It also turns out that the responsibility to self is the sine qua non for all the others, and that this is a function of personal character—honesty, integrity, self-discipline and a sense of duty—all qualities which are unlikely to be taught or mandated. Moreover, if these qualities are not present, the likely result will be poor or incompetent practice performance. It is seldom indeed that they can be acquired through education or by accumulating formal or mandated continuing education credits.

• *How does physician competence and performance relate to the practice situation?* In medical school physicians acquire a framework of basic knowledge and skills which are needed to enter virtually any specialty. In a sense their competence is plenipotential. Specialty training narrows this potential competence to certified competence in a particular specialty while at the same time the potential for competence in other specialties diminishes. During a lifetime of practice further narrowing takes place until each individual physi-

cian develops an essentially unique individual practice which may be shared by a few other physicians at the most. A physician is expected to be competent and able to perform competently at whatever level of practice differentiation he or she may have reached at any particular time.

• *Are knowledge, skills and good character all that are necessary for continuing physician competence?* It is becoming recognized that continual learning, though essential, is not sufficient. A competent physician must also take into account any personal limitations due to mental and physical aging processes, and also attend to whatever stress factors may be present in his or her own personal or practice life. Many are coming to believe that physicians owe it to patients, peers and the public to maintain mental and physical competence (some might say fitness) and to practice only within this competence. This also suggests attention to personal life style and habits of work and recreation.

There seem to be quite clear messages emerging from such considerations as the above. Physician competence and performance are far more an individual matter than many might first suspect. Neither is ever static. Rather what constitutes competence and competent performance continuously changes with medical progress and is different for each stage in the continuing differentiation of each physician's practice, and therefore for each individual practice situation at any given time. It develops that the focus of responsibility for maintaining competence and also for monitoring performance actually lies with each individual physician. It seems reasonable that soon the trend will be toward more self-study of competence and performance and more self-directed learning to maintain competence and to improve performance. It appears that the role of professional educators (including academia) and professional organizations will be more to assist with self-study of performance and with self-directed learning or behavior change, in a way much as power-assisted steering in an automobile may assist the self-directed driver to stay on the road and reach his destination. The role of government will be more to promote these self-directed activities, encourage professional and academic support of them, and then to concern itself primarily with the identification, elimination, or rehabilitation (when possible) of those relatively few physicians who cannot or do not practice within a framework of accountability and are found by legal processes to be unfit for the responsibilities of patient care.

—MSMW

Chlamydiae: Exotic and Ubiquitous

During the 1970's *Chlamydia trachomatis* received attention.[1] The report by Covelli, Husky and Dolphin elsewhere in this issue serves as a useful reminder that the other species within the genus, *C psittaci,* is still with us. Psittacosis in humans is contracted by exposure to infected avian species. The clinical spectrum is quite broad; many patients will have a disease which cannot be distinguished clinically from Legionnaires' disease. The two diseases, however, can be diagnosed and readily differentiated by serologic testing. Although infections in humans can be contracted from exposure to feral birds, most infections result from exposure to pet birds or from occupational exposure in the poultry industry. Occupational exposure is difficult to control but many chlamydial infections in exotic pet birds could be prevented if the birds received effective chemoprophylaxis before sale. Exotic avian species imported into the United States are required to undergo a quarantine during which they receive chlortetracycline in their feed. Unfortunately, this system is an administrative failure. There is no supervision to insure that the birds receive adequate amounts of the drug. Routine monitoring of blood levels, to assure that adequate chlortetracycline concentrations are obtained, would probably prevent dissemination of infected birds and subsequent human infections.[2]

Psittacosis in humans is relatively uncommon—approximately 100 cases were reported to the Center for Disease Control (CDC) in 1979. Human infections with *C trachomatis,* however, number in the millions. In the past decade many of the clinical epidemiologic studies of *C trachomatis* infections stressed their etiologic role in 30 percent to 50 percent of nongonococcal urethritis (NGU). NGU has received much attention because it is a clinical syndrome that can be reasonably well defined. We are now reaching the stage where we can appreciate that NGU is probably least im-

portant among infections with *C trachomatis* in humans. As Holmes[3] has stressed, the clinical spectrum of sexually transmitted *C trachomatis* infection virtually parallels that of gonococcal infection. Thus, chlamydial infections in men are associated with urethritis and epididymitis; in women they are associated with cervicitis, urethritis, bartholinitis and acute salpingitis. In the United States the prevalence of chlamydial infections is undoubtedly higher than that of gonococcal infections. Much emphasis has been placed on the socioeconomic distribution of NGU versus that observed for gonococcal urethritis. It has been shown that NGU is more common in upper socioeconomic classes, whereas gonococcal infections are more common in lower socioeconomic classes. Although this is true, it is, unfortunately, also potentially misleading because it represents relative distributions. The high-risk groups for chlamydial infection are, in fact, the same high-risk groups for other sexually transmitted diseases. Chlamydial infections and their complications occur at greater rates in lower socioeconomic groups.

It is important for clinicians to be aware of the clinical spectrum and prevalence of chlamydial infections because they are easily treated. Tetracyclines are the drugs of choice (2 grams per day for a week or 1 gram per day for two weeks) with erythromycin or sulfonamides being alternates. Sexual contacts should be treated as well. Unfortunately, most clinicians do not have access to tissue culture laboratories that can isolate chlamydiae. Thus, diagnosis of NGU, or a presumptive chlamydial infection, is often made by ruling out gonococcal infection. However, this approach will miss many chlamydial infections because 20 percent to 30 percent of men and 30 percent to 50 percent of women with gonorrhea also have chlamydial infections. These double infections are clinically relevant; penicillin treatment will cure gonorrhea, but in men with chlamydial infections, postgonococcal urethritis will develop. Recognition of this situation has led CDC to place tetracycline (2 grams per day for five days) as one of the recommended treatments for gonorrhea. This regimen is adequate for gonorrhea and will presumably prevent development of postgonococcal urethritis. Compliance may be a problem with some patients. Oriel[3] has recommended that men with gonorrhea receive penicillin with a five-day course of tetracycline started the next day. It is to be hoped that the routine use of antichlamydial therapy will decrease the prevalence of these infections.

In addition to its role as a genital-tract pathogen, *C trachomatis* is recognized as a leading cause of perinatal morbidity. Approximately 70 percent of infants exposed to chlamydiae during passage through the birth canal will acquire a chlamydial infection; 30 percent to 50 percent of the exposed infants will develop conjunctivitis and 10 percent to 20 percent will develop pneumonia. Depending on the population studied, maternal infection rates for *C trachomatis* have ranged from 2 percent to 25 percent. Thus, from 1 percent to 10 percent of newborn infants will develop chlamydial infections that require medical attention.

Clearly, chlamydial infections represent a major public health problem and deserve a more concerted effort toward their control. These efforts should be directed at chlamydial infections of the female genital tract. Women are at greatest risk for systemic complications and are the reservoir for transmission to neonates and men. Unfortunately, clinical signs pathognomonic of chlamydial infection do not develop in women.

We should not be complacent about our current knowledge of *C trachomatis* infections. Given the revelations of the past decade, it is predictable that further expansion of the clinical spectrum will take place in the next ten years. The role of chlamydiae in the following conditions must be defined: respiratory disease and pneumonia in children and adults; maternal complications of pregnancy; nongonococcal proctitis in homosexual and heterosexual populations, and enteric disease associated with chlamydial infection of the gut. Each of these clinical conditions represents a disease complex in which involvement of a chlamydial agent logically can be expected.

The simplest way to view the pathogenesis of chlamydial infections is to consider them as parasites of columnar epithelial cells. In anatomic sites, where they reach these cells (either by autogenous spread or by person-to-person transmission), they are likely to cause disease. These conditions are usually local but systemic spread may occur. A fertile area for research may be disease in immunosuppressed persons; experiments with animals have shown that local chlamydial infections may become more invasive if the immune response is suppressed.[4]

It will be interesting to see if further research efforts do expand the clinical spectrum of chlamyd-

ial infections. In any case, it is to be hoped that further research will provide simplification of laboratory techniques to permit routine diagnosis of these infections.

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Cuban Health Care

THE REPORT on health care in modern Cuba, to be found elsewhere in this issue, describes for yet another developing country what can be accomplished with centralized control.

As medical students, Campos-Outcalt and Janoff researched the subject and then made a brief but perceptive visit to that Communist nation which lies so close to our shores. Their description evokes admiration for what has been achieved in a relatively short time to improve the health of the people in that country. But at the same time something seems to have been lost or taken away. To be sure, both medical education and medical services are free and, by many measures, health seems to have improved. Yet the price for such improvement is living under a regime where the lives of persons appear to be almost totally regulated and supervised, and where even thought seems to be directed or controlled by the government.

One may well ask whether the accomplishments in health care may not be something of a travesty when so much in the way of human dignity and human potential has been lost to development and fulfillment. Yet this is the mark of powerful forces of conquest and entrapment which seem to be gaining substantial ground in today's world. In our own growing enthusiasm for health and health care let us not be trapped into sacrificing too much of individual freedom and personal fulfillment. So far we have not.

—MSMW

Paraneoplastic Syndromes: Something Old, Something New

THAT TUMORS PRODUCE HUMORS is no longer news. But it is no less impressive to see the paraneoplastic syndromes, from Dan to Beersheba, collected in one paper and comprehensively reviewed, as Stolinsky has done in the Medical Progress article elsewhere in this issue. He has reminded us that, recognized or not, the remote effects of tumors have been recorded for more than a century. And over the years we have come to learn that paraneoplastic syndromes are relevant to physicians in many subspecialties, to diagnosticians and to therapists, alike. Action resulting from an awareness that such diverse syndromes as hypercalcemia, inappropriate secretion of antidiuretic hormone (SIADH), hypoglycemia, erythrocytosis and nephrosis—to name but a few—may be due to a neoplasm, cryptic or apparent, can enhance in favorable cases a patient's life span and life-style.

Recently, something new has been added. As a result of investigations by the late Solomon Berson and by Rosalyn Yalow—who received the Nobel Prize for this work—radioimmunoassay has been perfected as a general method to permit the detection, with great specificity and sensitivity, of almost any protein.[1] We are now able to test the hypothesis long held by biologists, and restated so clearly in recent publications by Odell, Wolfsen and their colleagues,[2] that all neoplasms are capable of producing one or more (ectopic) proteins, not normally produced by their tissue of origin.

Radioimmunoassays, and their kin the radioreceptorassays, allow clinicians to go beyond analysis for proteins known to be responsible for a particular paraneoplastic syndrome, such as adrenocorticotropic hormone (ACTH) in cases of the Cushing syndrome or vasopressin in a tumor-associated SIADH. We can now look for, and indeed often find, tumors that produce proteins whose effects, so far as we can tell, are clinically inapparent. These are, if you will, paraneoplastic proteins in search of syndromes. Ectopic production of certain placental proteins, of calcitonin,

and of the common α subunit of the glycoprotein trophic hormones, to name some well-studied cases, are examples of such paraneoplastic "laboratory syndromes."

Because the study of in vivo production of ectopic proteins may be complicated by considerations of metabolic clearance, and simultaneous comorbidity or chemotherapy, some workers have turned to the study of human tumor cells in vitro. Systematic screening of these cell lines for a wide variety of proteins by Rosen, Weintraub and Aaronson,[3] as well as by Neuwald, Ruddon and their associates,[4] has turned up, as the hypothesis predicted, many new instances of ectopic protein production. Interestingly, this ectopic production is not random—some proteins were found surprisingly often, others not at all.

The latter observation confirms experimentally what clinicians have long suspected. As Stolinsky's review shows so convincingly, clinicians have associated the production of a particular protein with a particular neoplasm. Consider the peculiar predilection for vasopressin and ACTH production by oat cell carcinoma of the bronchus, as well as the striking prevalence of this cell type among patients with the Eaton-Lambert syndrome. For the epidermoid bronchial carcinoma, on the other hand, hypercalcemia is a common concomitant while the Cushing, inappropriate ADH and Eaton-Lambert syndromes are rare indeed.

Just as radioimmunoassay and radioreceptor-assay techniques have added a new dimension to the old notion of purely clinical paraneoplastic syndromes, so now do we need another breakthrough. We need to understand precisely how it is that tumors produce ectopic proteins at all, and what it is that determines which tumors shall make which proteins. Why is it, for example, that all normal fibroblast lines examined thus far produce the placental protein SP_1, but none produce placental lactogen or the α subunit, and only rarely produce the β subunit of chorionic gonadotropin?[5] Why do long-term cell lines established from malignant human neoplasms often produce the β subunit of chorionic gonadotropin, the common α subunit and SP_1, but do not produce detectable amounts of growth hormone or thyrotropin? Is our inability to find growth hormone due to failure of transcription and, hence, too little of its messenger RNA, or is it due to some unknown posttranscriptional process? The methodology of modern molecular biology is newly available to aid our search for answers to these questions. Perhaps the 1980's will yield new insights into the myriad of old but intriguing questions raised by the phenomenology that Stolinsky has so carefully assembled for us.

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CASE REPORTS

Refer to: Covelli HD, Husky DL, Dolphin RE: Psittacosis: Clinical presentation and therapeutic observations. West J Med 132:242-244, Mar 1980

Psittacosis

Clinical Presentation and Therapeutic Observations

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PSITTACOSIS is an uncommon cause of acute respiratory disease acquired after inhalation of dry excreta from infected psittacine birds, primarily parakeets and parrots. The disease in humans ranges from a mild febrile illness to a systemic infection resembling a severe influenza-like syndrome. Recently, there has been a progressive increase in reported cases per year with most patients giving a history of direct contact with treated and, presumably, noninfected caged birds.[1] We report a typical case of psittacosis, describing the usual clinical manifestations and commenting on the possible reasons for an increasing incidence.

Report of a Case

A 57-year-old previously healthy woman was admitted to hospital after a five-day history of shaking chills and high spiking temperatures, mild nonproductive cough, anorexia, nausea and vomiting. She said she had not recently traveled out of the country or been exposed to any ill family members.

On the initial physical examination the patient was very lethargic and confused, with a temperature of 40°C (104°F), a heart rate of 120 beats per minute, blood pressure of 120/70 mm of mercury supine, decreasing to 80/50 sitting. Examination of the chest disclosed decreased breath sounds, dullness to percussion and rales over the right posterior hemithorax. Other examination findings were within normal limits. Routine laboratory data disclosed the following values: Hemoglobin, 16 grams per ml; hematocrit, 48 percent, and leukocyte count, 9,800 per cu mm. The platelet count was within normal limits. The serum sodium was 148 mEq per liter; potassium 3.1 mEq per liter; chloride 117 mEq per liter; bicarbonate 22 mEq per liter; blood urea nitrogen (BUN) 15 mg per dl; blood glucose, 203 mg per dl, and alkaline phosphatase, 51 IU per liter. Serum glutamic oxaloacetic transaminase (SGOT) was 48 units per liter; lactic dehydrogenase (LDH), 293 units per liter, and total bilirubin, 0.4 mg per dl. Arterial blood gases drawn while the patient breathed room air showed a pH of 7.50, oxygen pressure (Po_2) of 83 and carbon dioxide pressure (Pco_2) of 19 mm of mercury. A roentgenogram of the chest showed a consolidating right lower lobe infiltrate with a small pleural effusion (Figures 1 and 2). Thoracocentesis disclosed 1,600 leukocytes per cu mm with a differential count of 17 percent polymorphonuclear leukocytes, 54 percent lymphocytes and 29 percent mesothelial cells. Pleural fluid LDH was 198 units per liter and pleural fluid protein was 210 mg per dl. No organisms were seen on Gram stain or acid-fast bacillus stains. Induced sputums resulted in nonspecific findings.

The patient was given 500 mg of erythromycin intravenously every six hours because Legionnaires' disease was suspected. She slowly improved while remaining febrile through the fourth hospital day. At this time repeat serum chemistries showed alkaline phosphatase, 162 IU per liter; SGOT 260 units per liter; LDH, 705 units per liter, and total bilirubin, 0.8 mg per dl.

A thorough history taken again at this time disclosed that the patient had recently purchased a parrot that died after a brief respiratory illness, approximately ten days before the onset of her symptoms.

The patient was discharged in good condition after a ten-day stay in hospital. She continued

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to take erythromycin orally for one more week. A month after presentation the patient felt well, all laboratory values had returned to normal and a roentgenogram showed that the consolidating pneumonia had resolved. Acute and convalescent serum titers for Legionnaires' disease were negative; however, complement-fixation titers for chlamydiae had a significant fourfold increase from less than 1:5 to 1:128 within two weeks. Close family members not residing with the patient had negative titers for chlamydiae.

The patient's first parrot and a second one subsequently purchased from the same pet store by her family died of a respiratory illness. Both birds showed classic findings of systemic psittacosis at autopsy and *Chlamydia psittaci* was isolated in cultures grown from specimens from each parrot.

Discussion

Psittacosis in humans results from inhaling *Chlamydia psittaci,* Gram-negative obligate intracellular organisms capable of independent metabolism. They have a discrete cell wall and are susceptible to antibiotics.[2] The common reservoirs for these organisms are psittacine birds (parrots, parakeets and cockatoos), with the more inclusive term *ornithosis* indicating that nonpsittacine species (pigeons, turkeys and ducks) are also potential carriers, especially in the United States. Most published cases have resulted from epidemics,[3,4] although in this country most cases are of a sporadic nature.[1,5] The estimated mortality ranges from 1 percent to 5 percent, with parrot and turkey strains being more virulent for humans. However, appropriate therapy in patients in whom the disease has been identified early can result in a fatality rate of less than 1 percent.[6] Most patients relate a history of bird exposure,[1,5] although the responsible animals may not have appeared sick or may have had only a mild illness. Person-to-person transmission has been reported, but is apparently rare.[7]

The disease typically presents, after an incubation of one to two weeks, as an acute illness manifested by a nonproductive cough, dyspnea, high spiking fevers, often greater than 40.6°C (105.1°F), and severe diffuse headaches. Frequently, complaints of pleuritic chest pain, blood-tinged sputum, myalgias and arthralgias are noted.[3,5] Patients with severe cases invariably have pneumonia, and some have clinical symptoms resembling typhoid fever, including the presence of bradycardia and rose spots.[5,6] Other significant complications may include invasion of the central nervous system with delirium and stupor being noted, as well as pronounced hepatic involvement during the initial septicemia which can result in features similar to those of acute

Figure 1.—Posteroanterior roentgenogram of the chest showing consolidating right lower lobe infiltrate.

Figure 2.—Lateral roentgenogram of the chest showing right lower lobe infiltrate.

viral hepatitis. Occasionally, pericarditis and fatal myocarditis have been reported.[3,5] Physical signs of pulmonary consolidation are frequent, with pleural friction rubs being reported in a number of patients. Hepatosplenomegaly is often described and occurs in up to 30 percent of the patients. Pericardial friction rubs, cervical adenopathy, pharyngitis and erythema nodosum have also been noted.[3,5,7]

Laboratory data typically are nondiagnostic, with leukocyte counts often being normal or slightly increased with a nonspecific differential. Liver function abnormalities resembling viral hepatitis have also been reported.[5] Sputum, if productive, is also nonspecific with only a few polymorphonuclear cells being seen on Gram stain, although the organisms may be isolated in two to 30 days depending on the sophistication of the culture techniques.[2] The complement-fixation test is group-specific, measuring antibodies common to all chlamydiae. Seroconversion, defined as a fourfold or greater increase in titer, is useful in the diagnosis of lymphogranuloma venereum and psittacosis. Other chlamydial disorders such as genital-tract infections typically produce nondiagnostic low titer changes.[2] Antibodies that usually appear in the second to the fourth week, however, may be delayed or suppressed if antibiotic therapy is initiated.[7,8]

Roentgenographic findings are variable. However, most reported cases present with segmental or lobar consolidating infiltrates (Figures 1 and 2). Hilar adenopathy and pleural involvement were common in one large series with a homogeneous "ground glass" appearance also being reported.[9] Roentgenographic resolution was often delayed averaging over six weeks before significant clearing occurred.[3,9] Drug therapy for this disorder has not been thoroughly evaluated, although tetracycline in a dosage of 2 grams per day for two weeks is effective with chloramphenicol being the alternate drug of choice.[7] Indolent responses to tetracycline are often noted,[5,8] possibly related to the various dosage schedules that have been advocated throughout the literature. Erythromycin is an effective agent against chlamydiae in vitro,[10] and in one case report resulted in rapid clinical improvement after penicillin failed.[11] The avian laboratory of one of the authors (R.E.D.) has repeatedly shown that chlamydial isolates from birds are sensitive to erythromycin and are eradicated effectively after a 21-day course of therapy.[12] Our patient, despite the lack of serological evidence of Legionnaires' disease, also showed a rapid response to erythromycin. Of note are recent reports emphasizing the close antigenic relationship between Legionnaires' disease and chlamydial psittacosis[13] and their similar clinical presentation.[10] Because a clinical distinction between these two unusual respiratory infections is impossible at present, a thorough history of bird exposure is essential to an early diagnosis. Serological testing would help determine the prevalence of these disorders in various communities. Further studies are needed to determine the usefulness of erythromycin in controlling suspected cases of either disorder.

A more important issue than which antibiotic to use for this disease is how to successfully identify, isolate and treat all infected birds entering this country. Present policies have resulted in the widespread release of birds infected with chlamydiae from quarantine stations despite attempts to administer antibiotics. The drugs are often given in a diet meal foreign to most birds,[12,14] resulting in the ingestion of subtherapeutic doses of chlortetracycline.[12] Continuation of ineffective therapy of infected birds while in quarantine is likely to result in increased dissemination of psittacine disease when the birds are released. This is substantiated by recent increases in reported human cases.[1] Early recognition of this disorder is crucial for the control of epidemics, the rendering of appropriate therapy for sporadic cases, and the identification and education of quarantine station and pet store personnel who may be releasing infected birds.

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Refer to: Hankins FD, DeSanto DA: Treatment of osteogenic sarcoma that had metastasized to the lungs—25-year survival of a patient. West J Med 132:245-248, Mar 1980

Treatment of Osteogenic Sarcoma That Had Metastasized to the Lungs

25-Year Survival of a Patient

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OSTEOGENIC SARCOMA is the most common of the primary malignant tumors of bone, occurs most often in childhood and adolescence, and is the leading cause of death from bone cancer in children. Treatment is based primarily on surgical ablation combined with radiotherapy and, more recently, chemotherapy. Metastasis is by the hematogenous rather than the lymphatic route, and death usually results from massive metastasis to the lungs.

Except for the relatively favorable outcome for treatment of the slow-growing variant known as parosteal sarcoma, for which curability with proper therapy approaches 100 percent, five-year survival from osteogenic sarcoma approximates 20 percent. Coley and Pool[1] in 1940 reported a five-year survival of 22 percent based on a study of 217 cases. Coventry and Dahlin[2] in 1957 reported a five-year survival rate of nearly 20 percent based on a study of 430 cases from the Mayo Clinic. More recently (1973), McKenna and Moore,[3] reviewing the material in the California Tumor Registry, reported absolute five-year survival figures of 20 percent for osteogenic sarcoma. At present, the term osteosarcoma is gaining acceptance as the designation for this tumor. This uniformity in survival figures is of more than academic interest because the sources are unimpeachable.

Although osteogenic sarcoma ranks as one of the most lethal types of cancer, it is not a hopeless entity as these figures show. Optimism in the therapeutic approach was characteristic of the Coleys[1,4] and bone sarcomas that appeared hopeless often responded favorably to combinations of surgical ablation, radiation therapy and treatment with Coley's toxins.

The development of metastasis to the lungs does not necessarily indicate a hopeless outcome. Surgical removal of a solitary metastatic lesion may prove as successful as removal of a primary lung neoplasm or metastatic adenocarcinoma. Unfortunately, metastasis to the lungs from osteosarcoma is often multicentric and bilateral.

We report a case in which a "palliative" resection of an osteogenic sarcoma of the left humerus was followed two years later by a palliative right upper lobectomy for metastatic sarcoma. The patient has survived the amputation for 28 years and the pulmonary resection for 25 years, and is now free of disease. So far as we are aware, this is the longest survival ever recorded.

Report of a Case

A 15-year-old boy was admitted to Good Samaritan Hospital in Phoenix, Arizona, on November 26, 1951, with complaint of severe pain in the left shoulder area. Earlier, in August 1951, he had had a fever following which his left arm was fractured by a kick in football practice. His arm was placed in an abduction splint. However, the pain became more severe and the boy was referred to Good Samaritan Hospital, where diagnostic facilities existed that were not available in his rural community.

A physical examination disclosed atrophy of the muscles of the left shoulder girdle with impaired function. X-ray studies showed "an area of destruction involving the left humerus just distal to the humeral head. There is soft tissue swelling over this area in which there are areas of calcification." Radiologic interpretation was "malignant bone tumor, possibly Ewing's tumor."

An exploratory biopsy was done on November 29. A tumor was found between the medial portion of the left deltoid and pectoral muscles. It was bluish, soft and hemorrhagic. A small specimen of tumor tissue was removed for frozen section study and reported as malignant. Permanent sections disclosed osteogenic sarcoma. The tumor was found to be large, pulsatile, hemorrhagic and corresponding to what Ewing[5] termed "telangiectatic osteogenic sarcoma." The patient's physician stated:

Investigation of this type of case would indicate that the

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outcome is practically hopeless, regardless of method of treatment employed. Most reported cases have died within a few months of pulmonary metastasis. Chest radiographs taken at the hospital do not show evidence of metastasis at this time. Later on, if the condition becomes painful, a trial of x-ray therapy might be indicated.

This statement by a qualified orthopedic surgeon summarizes the views that were widely prevalent in 1951.

The patient was given mild analgesics and discharged to his home on December 18. In January 1952, he consulted a physician in San Diego and was referred to one of us (F.D.H.). Repeat x-ray studies of the left shoulder showed a destructive lesion of the left humerus, and repeat x-ray films of the chest at the time were negative for metastatic lesions. Because of severe pain, a surgical operation was scheduled. Before the patient was admitted to hospital conventional x-ray therapy was carried out (220/kv for a total of 750 rads).

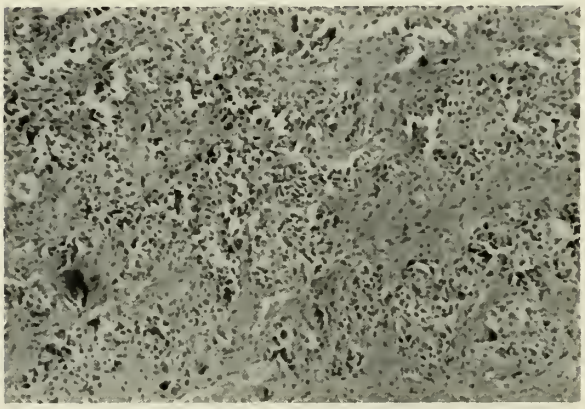

Figure 1.—Photomicrograph of representative area of primary tumor (osteogenic sarcoma). Note numerous spaces lined by and containing tumor cells with intervening solid tumor osteoid. (Reduced from magnification ×60.)

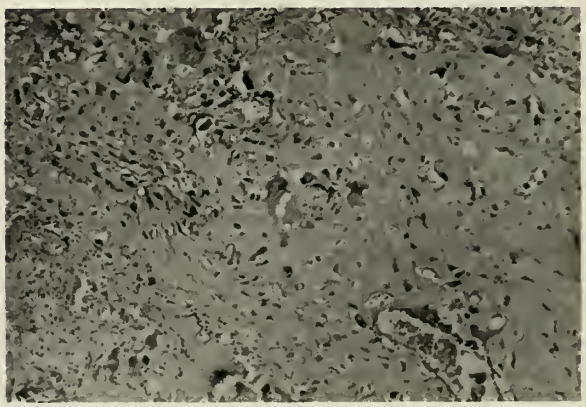

Figure 2.—Portion of solid area of a typical osteosarcoma, classic tumor osteoid. (Reduced from magnification ×120.)

He was admitted to Mercy Hospital and Medical Center, San Diego where left forequarter amputation was done on January 11. The entire left upper extremity, scapula and clavicle were removed, followed by a dissection of the axilla.

Pathologic Study

The head of the humerus and the metaphysis were replaced by a hemorrhagic tumor mass that measured 5 by 8 by 10 cm and extended into the adjoining soft tissues. The tumor was friable with focal areas of calcification. The glenoid fossa and scapula were uninvolved. There was pathological fracture of the metaphysis of the humerus and the defect was filled with soft, hemorrhagic tumor tissue.

Findings of a microscopic study done by one of us (D.D.S.) were typical of anaplastic telangiectatic osteogenic sarcoma. Large tumor cells lined blood spaces and areas of tumor osteoid were present (see Figures 1 and 2). The classification was that of Ewing[5]—the accepted standard at that time. Fourteen axillary lymph nodes were free of tumor cells.

Subsequent Treatment

The patient was discharged on January 19, and his condition was followed by his personal physician. He was able to work during 1952, and returned to Arizona where he entered college. He returned to San Diego for routine follow-up on August 11; examination results indicated that he was clinically well and asymptomatic. Routine x-ray films of the chest on August 12, 1953, however, disclosed a "2.0 cm coin lesion just below the first left rib. The rest of the lung fields are clear. The heart and great vessels are normal."

The family was advised that the patient's prognosis was hopeless, but that the quality of his life might be improved somewhat if right upper lobectomy was done. With little hope for a favorable outcome, the family, nevertheless, accepted the advice and gave informed consent for the operation.

On September 1, the patient entered Paradise Valley Hospital and Sanitarium in National City, California, and a left upper lobectomy was carried out (by F.D.H.). The left lobe measured 11.0 by 9.5 by 3.5 cm. Two tumor nodules, 3 cm and 1 cm in diameter, respectively, were present on gross examination, although only one had been identified in the radiographic studies. Findings of a microscopic study of the metastatic lesions were

typical of osteogenic sarcoma and virtually identical to those of the primary bone lesion (see Figure 3). Postoperative roentgenograms of the chest (September 11) showed no additional metastatic lesions. The patient has been seen at regular intervals since then, and his progress has been followed by the Tumor Registry of Mercy Hospital and the California Tumor Registry. He is now a successful educator with a PhD. Results of an examination in December 1978, showed no evidence of disease.

Discussion

Survival from osteogenic sarcoma is uncommon, but survival from osteogenic sarcoma that has metastasized to the lung is even rarer. Metastatic lesions are usually multiple and massive, and resection is surgically unfeasible. However, localized pulmonary metastasis is an indication for resection or lobectomy.

Sweetnam and Ross[6] in 1967 reported a series of 12 cases of bone cancer in patients being treated at a small group of hospitals in the United Kingdom. Their criteria for resection were (1) the primary growth must have been entirely eradicated, (2) there must be no other detectable metastatic lesions and (3) the lesion in the lung must appear to be solitary. All of these criteria were fulfilled in our patient.

Their series included six cases that were diagnosed as osteosarcoma. The longest survival among their patients with metastatic osteosarcoma was 13¼ years. One of the patients (case 11) died seven years after resection without evidence of metastasis at autopsy. Most of their patients, however, died within seven months to 1¼ years.

According to Sweetnam and Ross, the greatest problem confronting a thoracic surgeon is the decision as to the optimum time for surgical intervention. Should one operate at once, or should one delay the procedure briefly to see whether additional metastatic lesions develop? This question is unanswerable at present, but consensus favors a prompt secondary operation. The role of chemotherapy, using massive doses of methotrexate followed by citrovorum factor rescue, is advocated. It appears promising as a means of preventing the development of pulmonary metastatic lesions or treating them after they have developed. Dunn and Dehner[7] in 1977 reported a series of 72 patients with metastatic osteosarcoma to the lungs who were treated with intensive chemotherapy and pulmonary resection. Five-year survival of patients from their original amputation was 33 percent. These statistics suggest an overall improvement in prognosis when compared with the 20 percent survival figures from other sources.

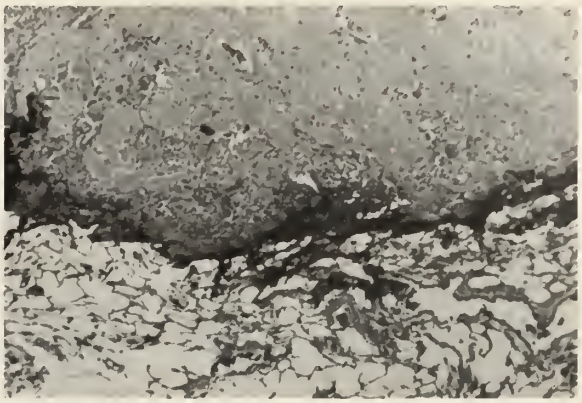

Figure 3.—Portion of metastatic lesion of the lung, histologically similar to the tumor specimen shown in Figure 2. (Reduced from magnification ×40.)

The evolution of therapy for osteogenic sarcoma has undergone an interesting historical cycle. Ferguson[8,9] advocated delay in amputation preceded by x-ray therapy. In his review of 400 cases of osteogenic sarcoma, in the Registry of Bone Sarcoma of the American College of Surgeons, Ferguson concluded that delayed amputation preceded by irradiation improved survival statistics. He reported a five-year survival rate of only 14 percent when amputation was done early as against 40 percent when amputation was delayed. He had no rational explanation for this disparity in end results. Those who have disputed Ferguson's conclusion claim that the most highly malignant cases occurred in patients in whom surgical operations were done early in the course of the disease. Ferguson's findings are quoted for their historic value.

Comment

The two small tumor nodules that were removed by lobectomy from our patient in 1953 were, undoubtedly, colonized by cells that were present in November 1951. This sheds light on the doubling time of osteosarcoma cells. Frei[10] has estimated that 1 gram of tumor tissue is invisible and contains 10^9 cells. A tumor nodule 3 cm in diameter, as in this case, developed in approximately 24 months and was composed of an estimated 27 billion cells.

Intensive chemotherapy,[11] which is now carried out prophylactically for the prevention of metastasis to the lungs, holds the potential of destroying small cell colonies that are invisible and clinically unrecognizable. In cancer centers where patients with osteogenic sarcoma are more common, it is becoming the treatment of choice.

Summary

The authors report a seemingly hopeless case of osteogenic sarcoma, occurring in the left humerus of a 15-year-old boy, that was complicated by pathological fracture. A palliative forequarter amputation was succeeded approximately two years later by the development of pulmonary metastatic lesions. A palliative lobectomy was done at that time, which was one of the first such procedures undertaken for this disease. The patient has survived the original operation 28 years and the lobectomy 25 years, and is now free of disease. This appears to be the longest survival recorded for a patient treated for an osteogenic sarcoma that had metastasized to the lung.

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Biofeedback for Mild Tinnitus

BIOFEEDBACK IS REALLY a type of self-hypnosis to help you live with your tinnitus in a better way, and patients are usually treated with six 20-minute treatments. We find that the patients who are somewhat high-strung and emotional might be able to live with their tinnitus if they were more relaxed. These are the patients who benefit from this type of treatment—not the ones who have a loud tinnitus that would disturb anyone.

—JACK L. PULEC, MD, *Los Angeles*

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 11, No. 16, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Orthodox Medicine Humanistic Medicine Holistic Health Care

IN THE December 1979 issue the editors of THE WESTERN JOURNAL OF MEDICINE began a forum for dialogue and discussion of orthodox medicine, humanistic medicine and holistic health care. The forum was initiated with statements by persons known to have an interest in and knowledge of this subject. Readers are invited to submit their views constructively and succinctly. As many as space permits will be published in future issues of the journal. At an appropriate time all of the material, published and unpublished, will be collated and, if possible, a distillate will be prepared to summarize the dialogue and discussion.

—MSMW

The Needs and Qualifications of Physicians

ROGER O. EGEBERG, MD

"I AM AFRAID there's nothing more I can do for you." (Said in so many words, or with the raising of the shoulders or the hands or the use of the eyes, to a patient with inoperable cancer.)

"You're not getting any younger, you can expect it at your age." (Said to an older patient with a stiff knee, a painful hip or an aching shoulder.)

"Sure your father is depressed, lots of older people are depressed, I can't do much to make him happier."

These expressions—far, far too common—reveal the attitude of many doctors educated in an era of greatly improved diagnostic procedures and an associated wealth of therapies. Lack of an appropriate treatment, inability to take positive action is something doctors now find it difficult to face. "If I can't cure it with pills, needle or knife, I had better get on to those patients I can cure." How many busy doctors of today would hate to admit that this lurks in their minds?

When I was a boy the doctor came to the home, if necessary, where he looked, felt, listened and sniffed, laid a hand on my head, took my mother by the arm as they walked out of the room, left some medicine, shared the worry, reassured the family and created an aura of hope for improvement. And he or she (yes, our family doctor was a woman) probably returned the next day.

When it was clear that my grandmother was ill with terminal cancer, was when her doctor's work really began. He gave comfort, relief of pain, wholehearted relief of pain, and he gave time, time to answer questions, to explain what he knew, to share the anxiety, the worry and the sadness; time to stroke a brow and to hold a hand.

That is the heritage, still felt, of the horse and buggy doctor. An allopath whose allopathic therapies had so very little to offer. He taught us what they then knew about prevention and encouraged and exhorted us to keep well. Since his time the scientific knowledge of medicine has probably increased tenfold. It has been estimated that it doubled between 1940 and 1960. Our understanding of the cause of disease, the pathology of any disease, our richness of modalities of treatment and our accomplishments in rehabilitation have given us tools, weapons with which to fight our enemy, disease. But this very array of power, resulting in a sense of power to do battle with specific disease states has changed our target, and we have lost our ally, the patient, both ally and battleground.

Perhaps now the doctor sitting at a sick patient's bedside does not touch the patient, does not ask many questions, does not listen very long; perhaps he wonders if he might gain more insight into the illness by going to the library to scan the literature; perhaps he feels that there is not much he can do in the way of prescribing, so why stay. This doctor is really a distant relative of the allopathic physician of the turn of the century. Our allopathic medicine, because of advances in biologic knowledge, has been subdivided into many specialties. Has not medicine itself become with its greater depth a narrower specialty than it was 80 or 90 years ago? Have we not stripped off to a large degree a working concern for the patient's immediate environment, the conditions under which he or she lives? Are we really interested in

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what patients eat and how? Now that it is not a necessary part of living are we suggesting exercise for its own sake and putting that suggestion across? Are we adequately interested in the many facets of the patient's pattern of living that would help to keep him or her healthy? Are we creating in the patient a sense of personal responsibility for achieving and maintaining his potential state of health or well-being? All of this does take more time. It is not easily measured so it is not paid for by Medicare or Medicaid or private health insurance under present methods, and they should carry their share of the blame. The occasional house call, more intelligent listening, the broadening of the field of questioning, the viewing of the patient in a different light—all of these are important to the full care of a patient and they are missed by so very many. These glimpses of the allopath of the turn of the century and the one of the present day—glimpses only, exaggerations possibly, are the central theme of discussions of humanistic medicine and are equally pertinent to the discussion of the practice of medicine by committee which is often implied in the description of holistic health care.

The ideal horse and buggy doctor furnished all that allopathy had to offer and much that it now fails to use or indeed shows interest in. Is that not what we really want back when we speak of humanistic medicine? It is a very important part of treatment, this considering the patient as a person in need of many things, going beyond what medicines or operations can cure. Is that not the core of humanistic medicine no matter how practiced? Many, possibly most, physicians try to fill these needs. If they did not, I dare say there would be a much greater distress about the practice of medicine. Of course, there are those who do not, and be they only 20 percent they would amount to 60,000 physicians in the United States, enough from whom to draw tremendous numbers of horrible examples. Be they 15 percent or 20 percent they are among us. Why? Is it the training or is it the awesome wealth of information, knowledge, in our field or is it the quality of persons chosen to study medicine? Medical schools being as departmentalized as they are, training is certainly part of the cause. Introductions and overviews do not usually carry a feel of the olympian view needed. The wealth of knowledge available certainly plays its role. However, the fundamental change is in the students chosen, the selection process. I do not believe it requires an I.Q. of 135 to 140 to practice good medicine. I do not think that straight A's in chemistry, physics, botany or biology are a prime requisite for a good physician. There is a fallacy in the criteria used for choosing men and women for medical school.

Some decades ago, the federal government wisely decided to support basic biologic research in this country. Looking for a home for such work the government through the National Institutes of Health turned to the medical schools—who were happy to receive the investigators. Increasingly, the government allowed these researchers to teach; at first only 10 percent of their time and later with a more relaxed attitude they passed that decision to the schools. They thus honored research but did not in any commensurate way, that is financially or in professional stature, honor teaching.

With free or virtually free teaching and the prestige and excitement of research the medical schools in a generation were taken over by research. This was certainly to the great good of mankind, but not necessarily so for individual patients. In time, in a couple of decades, the admissions committees were made up of people in the field of research. In their hands, possibly as an easier sifting mechanism, the prime requirements for entry into medical schools—the basic requirements—became grades and aptitudes; grades and aptitudes in science. This focus was possibly born of the hope of getting a brilliant young research associate or a later Nobel laureate. It has been hard on the broader ranging man or woman, less academically brilliant perhaps or less grade motivated, even though such a person's patience and love of individual human beings might stand out like a beacon compared with so many of the 3.7 or 3.8 smooth interview applicants. Those who are chosen, unless indeed they do remain in research, are likely to find practice a bit stultifying, even boring, after 15 or 20 years. They miss out on the reward that would continue to come to one who gets an instinctive satisfaction and joy in helping others. And they become interested to an increasing degree in other pursuits, from motorboats through planes to the building of office buildings.

From personal experience, I would say that the interviews to plumb the breadth and depth of applicants are not worth very much, for the sophisticates put on a consummate and calculated act. As those students, little motivated by the human problems in medicine, progress through

medical school, they shed or lose that show of concern that they earlier seemed to have.

The increasing writing and talk—not clamor—about humanistic medicine and holistic health care is nurtured by those many patients who feel a lack of personal concern on the part of physicians. This is real and is based on a felt need. As such a movement gains credibility it attracts a deluge of hocum artists who profess concern for patients as whole persons, who are quick to decry good medicine, who *have* little or no basic knowledge and who display a pseudo-concern, claiming that they are humanistic or holistic. To those hangers-on or shirt-tail riders, I would say you are dangerous to your patients. To the profession I know and belong to I would say let us give thought to the whole spectrum of qualities that we think doctors should have—and let us bring such people into medicine. And to you serious students and practitioners of humanistic medicine I would say I wish you well and thank you for highlighting the unbalanced view of the needs and qualifications of physicians.

Holistic Medicine for Neurosurgeons

ROBERT RASKIND, MD

I READ WITH INTEREST the several articles on holistic health care, humanistic medicine and orthodox medicine, and I must say that I am not fully able to grasp the concepts implied.

More specifically, I have been criticized by several persons who are proponents of these dogmas both in my community and in the surrounding communities for my rather naive and, as they state, "inappropriate" approach to diseases of the central nervous system.

We deal with a number of intracranial space-occupying lesions from which, without their removal, a patient would either be dead or seriously impaired neurologically. As an example, I have one case of a 38-year-old man with a 3½-year history of what looks like an infiltrating glioma both on CAT scan and the subsequent angiograms. Needless to say, the standard neurosurgical advice in such a situation would be craniotomy for excision of the lesion.

My critics tell me "that we should not treat the tumor, but should treat the patient." This makes it very unclear to me as to exactly what my role in this patient's care should be. They have strongly advised the patient and his family against operative intervention, and the questions I ask are (1) How can we go about preserving this patient's life and (2) how can we go about alleviating his symptoms and preserve what neurological function is left without a direct attack upon the neoplasm?

There have been some equally vehement criticisms about the methods of dealing with life-threatening head injuries.

It would be helpful indeed if some of the advocates of holistic and/or humanistic medicine would give me guidelines for management of these life-threatening conditions.

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Teaching Medical Students to Stay Healthy

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MUCH OF THE DISCUSSION in the forum on "Orthodox Medicine, Humanistic Medicine and Holistic Health Care" in the January and December issues actually dealt with the widening gap in Medicine between technological treatment of disease and promotion of health. An interesting and important aspect of this division occurs within Medicine: the health status of medical students.

Medical students are like the shoeless sons and daughters of the cobbler—so close to the institutions devoted to the study of health care, yet denying their own mortality, and living a lifestyle which places them at high risk for many diseases. They work exceedingly long hours, eat an abundance of convenience and fast foods, and study under constant stress. As a group, they usually get insufficient sleep and do not have enough time for exercise. This lifestyle is more destructive

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than we would recommend even for the most robust of our patients. It is to the students' benefit that they are able to seek psychiatric counseling during their four years in medical school, and many of them are indeed compelled to utilize psychiatric services.

Clearly, they are learning from us, their teachers, that this type of lifestyle is required for at least four years of medical school and an additional three to four years of residency training, and perhaps is acceptable in practice. Often these students are in the position where they must divide precious few hours between study and time with their loved ones. Believing that one must begin with an ideal to end with an ideal, we are certainly missing the mark in producing physicians sensitive to the role of lifestyle and health promotion in their patients. Physicians find themselves at greater risk for suicides, drug addiction and alcoholism. Perhaps starting to teach medical students about health promotion could give them an opportunity to learn new coping skills.

It has been said that medicine is the only profession that labors to destroy the reason for its existence. Yet the average person might think that modern medicine acts quite the opposite in building more expensive and sophisticated machines to keep the critically ill alive. With medicine's incessant striving to find better diagnostic techniques and more effective treatment we have become almost fixated on technology and curing and have largely ignored prevention and health promotion.

At the Department of Family Practice of the University of California, Davis, School of Medicine, we are very interested in restoring a balance to the medical education process between learning about disease and exploring methods to keep people healthy. We believe it is essential for both patients and medical students that a strong health component be included in the medical school curriculum. We believe that in teaching students about taking care of themselves, they will learn to apply these lessons to their patients. Encompassing this idea, we developed an elective course for second year medical students called "Health Promotion for Medical Students and Their Patients."

The course begins with a thorough health inventory of each student. This includes diet, stress level, fitness, health risk assessment and psychological status. We also gather information on how their work (medical school) affects their health. The resulting health profile is then used in formulating a health prescription for each student. This includes relaxation, stress reduction, improvements in diet, exercise program, weight reduction and the like. Over the 12 weeks of class, the students are required to follow a monitored personal health promotion program. A health educator works with each student to assist them in their individual programs. We also provide each student an opportunity to practice what he or she has learned with a patient and family. Our goal is that the students will learn about health maintenance for themselves and their future patients. After the class has been completed, the students are reassessed. It is our contention that if physicians are to play any significant role in their patients' health maintenance, then medical schools should provide opportunities for students to practice healthful behavior themselves. We hope that teaching medical students about health is an idea whose time has come. Perhaps this attitude is too optimistic but "there is no sadder sight than a young pessimist" (Mark Twain).

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Peripheral Atheroembolus Following External Cardiac Massage

TO THE EDITOR: The potential complications of external cardiac massage during cardiopulmonary resuscitation are many. Well described in textbooks,[1] these include such complications as rib fracture, pneumothorax and fat embolism. We wish to report a case of embolic occlusion of the popliteal and distal arteries following external cardiac massage.

The vast majority of spontaneously occurring arterial emboli arise from the heart and are thrombotic in nature (that is, mural thrombus).[2] Emboli from atherosclerotic aortic plaques were first predicted by Flory in 1945[3] and later shown to exist by Hoye and co-workers in 1959.[4] This phenomenon is now well described as occurring spontaneously.[2,5,6] In our review of the literature (MEDLINE search), we found no instances of atheroemboli in connection with external cardiac massage.

Figure 1.—Section of embolus showing fibrin, aggregated blood elements and cholesterol clefts. (Hematoxylin and eosin stain, reduced from 40×.)

Report of a Case

A 70-year-old man arrived at the hospital following prolonged cardiopulmonary resuscitation (CPR) with external cardiac massage and electric defibrillation. He had collapsed while working and received immediate external massage, lasting 15 minutes. Eight defibrillation attempts with 320 watt seconds were required before sinus rhythm was restored. On arrival at the hospital, the patient was conscious and complained of pain and coldness in both feet. Physical examination showed a pulse of 90, regular, and a blood pressure of 130/80 mm of mercury. Lower extremity findings were consistent with bilateral popliteal-tibial arterial occlusions.

After heparin was administered, thromboembolectomy of both popliteal-tibial systems via a popliteal approach was carried out. Approximately eight hours elapsed between cardiac resuscitation and embolectomy. Histologic examination of the embolic material showed the presence of atherosclerotic cholesterol emboli (Figure 1).

The patient made a good recovery. Postoperatively, transient renal failure developed secondary to myoglobinuria from skeletal muscle necrosis. Results of serial electrocardiograms and cardiac enzyme determinations were compatible with acute myocardial infarction at the time of admission. At the time of the patient's discharge, however, cardiac and renal function were good,

and there was no evidence of peripheral arterial insufficiency.

Discussion

Embolization in this patient occurred immediately after (or during) CPR with electric defibrillation and external cardiac massage. The presence of cholesterol in embolic material excludes the heart as a possible source of origin[2] and implies that the arterial circulation is the source. In this case, with involvement of both lower extremities, and no apparent involvement of cerebral or upper extremity vessels, the source was presumed to be the proximal arterial tree, and most likely the descending thoracic aorta.

The only reported case of atheroembolus following CPR involved the anterior descending branch of the left coronary artery.[1(p427)] In that case, direct injury to the artery with subsequent embolization of the atherosclerotic plaque resulted from external cardiac massage. We report this case to show that atheroembolic occlusion of peripheral arteries can occur as a result of blood vessel trauma during external cardiac massage.

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Modern Medicine and Hospital Chaplains

To the Editor: A definition of health is not just the lack of disease but it is the optimum functioning of body, mind and spirit. In spite of this, not enough attention is given to the spiritual aspects of health in modern medical care. Doctors are trained more in the physical and psychological aspects of health and not at all in the spiritual. Furthermore, the mechanization of medical care has encouraged medicine to focus on physical health. Hospitals which were originally organized by religious groups are now more of a facility for the machines necessary for medical care; and, instead of religious organizations, hospitals are now publicly or privately owned. This leaves the spiritual influence out of medical care.

Yet, there is an increasing need for spiritual health care. The growth of emergency room medicine has its own need for spiritual help during crises. The whole concept of life support systems and the prolonging of life has complicated physical medicine and requires spiritual consultation. Dying, itself, is no longer considered a terminal event but a part of life. Therefore, much needs to be done spiritually for patients during the process of dying and for relatives after death has occurred. The increased use of organ transplants not to mention genetic engineering all require spiritual consideration before being utilized. Even the complicated concept of medical-legal medicine would be influenced in a positive way by involving the spiritual aspect of health care. Perhaps abortion would not be allowed today if modern medicine gave spiritual health care its due. Why is it we do not have hospital chaplains to help with these needs?

Probably the biggest reason we do not utilize hospital chaplains is that doctors have great control of hospitals and doctors do not understand how properly-trained hospital chaplains can help. A chaplain trained in clinical pastoral education can help the doctor treat his patient without complicating the medical care and without any increase in cost. A full-time hospital chaplain is a member of the hospital staff. He has been trained at a clinical pastoral education center (CPE) and he knows more than most chaplains about medical problems. His main job is to enable and to facilitate the job of clergy in the community who come to see their own parishioners. He notifies local clergy when their patients are in the hospital and he helps them to understand the medical problems involved. The hospital chaplain's other duties are to counsel and educate the hospital staff so they can better understand the psychological and spiritual feelings of their patients. The hospital chaplain also participates on tumor boards and medical ethics committees. Periodically, he conducts seminars on medical and spiritual topics for the hospital staff. Finally, people need spiritual help whether they are well, sick or dying. The hospital chaplain is available to provide these spiritual resources whenever they are needed. The reason hospice centers are be-

coming so popular is because hospitals are not meeting all the needs of their patients.

Hospital chaplains have been shown to improve the well-being of hospital patients. Studies have shown that patients do not generally ask for a chaplain when they are sick; however, when one is provided they are grateful that the service is provided. The patient's satisfaction is what the hospital is after and the cost in this case is minimal. Spiritual counseling improves the health of patients and staff. It improves the relationship among hospital staff, patient and physician. Modern medicine should improve the care of spiritual health and should utilize hospital chaplains in doing so.

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Costs of Cardiopulmonary Resuscitation

To the Editor: The October 1979 issue contained the article "Cardiopulmonary Resuscitation in a University Hospital" [West J Med 131:344-348] by Drs. Hahn, Hutchinson and Conte.

In calculating the costs of cardiopulmonary resuscitation it would be more reasonable and informative to include the cost of care beyond the time of resuscitation for the 81 percent who failed to survive to discharge. It would be interesting and valuable if Dr. Hahn and co-workers could review their cases and determine those costs. Whatever the costs might be, they might well be considered modest in relation to result.

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PSRO: Views of an Anti-PSRO Physician

To the Editor: In the November 1979 issue, Dr. Alan R. Nelson ("Perceptions on PSRO") and Dr. Paul J. Sanazaro ("PSRO, Politics and Quality Assurance") discuss the current status of the Professional Standards Review Organization (PSRO) program. Briefly, the doctors conclude that physician members of a PSRO find themselves positioned as judges of their colleagues' practice of medicine in terms of controlling cost instead of controlling quality. Further, in the process, they are intervening intimately in the practice of medicine; that is, they are telling a physician what service he may or may not offer his patient on pain of no payment to physician or hospital.

Despite their complaint about the PSRO program, Drs. Nelson and Sanazaro urge physician members to continue with it. This advice stems from their belief that the PSRO is the sole area in which future regulation of health care may be influenced by practicing physicians. Dr. Sanazaro goes even farther and advises that government is now in permanent partnership with physicians and hospitals in "quality assessment and quality assurance." This advice, to continue support of the PSRO despite its evolution contrary to initial hopes, is debatable. I think the problem arises from undefined concepts, from premises which are not a priori, and from logic paths that do not inexorably follow.

Let me start first with the undefined concepts. The big one here is quality. Can a practicing physician tell me what *quality care* is as it relates to individual patients? Is it the demand that a patient be seen in the office, or handling a complaint on the telephone? Is it prescribing antibiotics for a patient with an upper respiratory infection, or getting a throat culture first? Is it early or late admission to hospital for a patient with a suspected myocardial infarction? Is it an austere or a rich use of the hospital laboratory service? Is it four days or six days in hospital after a prostatectomy? Is it alternative birth centers? Is it a coronary bypass procedure on a 78-year-old otherwise in good health? Is it a procedure on a 78-year-old with a transient ischemic attack? With one stroke? Is it the overall mortality and morbidity record of a practitioner, or is it the neatness of his hospital records? After the PSRO has defined quality, perhaps it could define "overutilization," "underutilization," and even "fraud and abuse."

Second, the premises on which the PSRO legislation was conceived and authorized are not a priori. These premises assume partnerships that do not exist, such as between doctors and hospitals. They presume coinciding interests which in fact do not coincide, such as the care of the individual patient and the national budget. They assume that medical fraud is widespread, and that policing for this fraud will be cost effective without pilot studies to prove the assumption.

Finally, logic does not demand that doctors must participate within PSRO's in order to affect them. It is as logical that doctors can affect PSRO's from without.

Lest it be overlooked, it is important to emphasize that the historical role of a physician is

to act exclusively in the interest of his individual patients, and that this action should be contrary, if need be, to any other interest. It is consistent that a patient's interest might be contrary to the fiscal interest of the United States. It is certainly consistent that the interest of individual patient care as provided by individual doctors is outside the PSRO program, and not within it.

I think it is time for doctors to concede that the PSRO program is contrary to their historic professional role, and that it serves neither their interests nor the interests of their immediate patients. Therefore, doctors have no business in it. To the extent that PSRO's serve some other agencies' interests, let those agencies participate, let them be clearly identified therefore as working in their interests within PSRO's and let it be clearly identified that PSRO's are fiscal agents of the United States government with a potential adversary position toward the care of individual patients. This will align everyone in a proper position, physicians with their patients, fiscal agents with the government. Adversary positions will then be honestly confronted, and perhaps a more equitable cost distribution will evolve.

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Holism and the 'Team Approach'

To THE EDITOR: I have read with great interest the articles on holistic medicine in the journal. I have one major fear regarding this development: that traditional medicine in the future may suffer from a problem that confronts the Judeo-Christian religions at present, the invasion of cults.

I would prefer the simple term "team approach." In 1952 when the Child Development Center of Children's Hospital of San Francisco was started, the Crippled Children Services of the state made it one of its diagnostic centers. This gave us an opportunity to utilize several medical specialists in our diagnostic procedures. In addition to physicians, our staff consisted of physiotherapists, occupational therapists, a social worker, a psychologist, a speech therapist and an educator. The parents of the children formed their own group for mutual help and support. The staff had a weekly conference for discussion of problems related to the children, the parents and community facilities needed. In a recent issue of *New Horizons* (a publication of Children's Hospital), I see that a surgical group there has also organized a team for surgical services. Apparently holistic medicine has the same aim and intention, but, as mentioned earlier, I greatly fear the intrusion of undesirable cults.

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Acne and Teenagers' Diets

To THE EDITOR: It is paradoxical that in an issue featuring a forum on holistic and humanistic medical care there should be an editorial ("Acne —Fact and Folklore" Vol 131:547-548, Dec 1979), by Dr. Albert Kligman, that puts dietary care of acne patients in "the fogs of folkloric beliefs."

He states "youngsters can be rescued from the burdens of misbeliefs such as . . . avoiding . . . chocolates . . . soft drinks . . . ." Even the Supreme Court allows minority opinions so I would like to express a minority opinion. In 1966 I wrote an article for *Cutis* magazine in which I correlated population studies which attempted to show that people on a polyunsaturated liquid oil diet did not have as much acne as those eating a saturated solid fat diet. Since it is impractical to take 100 young people and keep them in cages on controlled diets, the main recourse is to do population studies.

Once the follicle is impacted and distended, it will not function perfectly even on a good diet. The comedones have to be removed and the follicles have to shrink down to capillary size again. So any dietary control involves two to six months at least.[1] Changing one saturated fat for another will not dispell the "folklore."

I admire and respect Dr. Kligman's contributions to medicine, and have just ordered tapes of lectures he has given, but I do reserve the option to disagree totally with him on diet. I agree chocolate is not a teenager's greatest enemy. It is the cow: first in her butterfat—butterfat in milk, in butter, in cheese, in yoghurt, in ice cream (and margarine is as bad if it is physically a thick hard fat)—and second in beef fat—in hamburger and hot dogs and sausage and steak. I agree that soft drinks have never caused a comedome —hard fats do that—but excess sugar lowers the opsonification index of polys and small pimples grow into "raging, inflammatory lesions," to quote Dr. Kligman.

So ice cream and malts and chocolate pack a double whammy—they plug up the follicle with

thick viscous fat (hot sunshine and sunburns help to thin it and improve it), and they interfere with the polys' ability to destroy acne bacillus so the small pimples get to be big cystic pimples.

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Cimetidine-Associated Thrombocytopenia and Leukopenia

To THE EDITOR: A brief case report is presented of a 52-year-old man with alcoholic cirrhosis and upper gastrointestinal hemorrhaging, who was treated with intravenous administration of cimetidine on two separate occasions during the same stay in hospital. Leukopenia and thrombocytopenia developed during both treatment periods.

He was admitted to hospital on August 23, 1978, with upper gastrointestinal bleeding. He had consumed no alcohol since July 21, 1978. The findings of a physical examination showed no abnormalities. Laboratory results on admission include the following: leukocyte count, 5,600 per cu mm; hematocrit, 28 percent; prothrombin time, 12.0 seconds (control 10.7 seconds); total protein, 6.0 grams per dl, and serum albumin, 3.4 grams per dl. Total bilirubin, alkaline phosphatase, serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) were within normal limits. Endoscopy disclosed large esophageal varices with adherent clots and erosive duodenitis. The patient was treated with 300 mg of cimetidine, given intravenously every six hours. During the next five days bleeding continued, and a total of eight units of blood was administered. He was given pitressin intravenously and received no other medication. On August 28, he was stable and eating, but the intravenous administration of cimetidine was continued. Two days later the leukopenia and thrombocytopenia were discussed, and cimetidine treatment was stopped (Table 1). On August 31, platelet and leukocyte counts were increased to pretreatment levels. On September 1, 36 hours after administration of cimetidine, a bone marrow

TABLE 1.—*Complete Blood Counts During the Patient's Stay in Hospital*

Date	*Time*	*Leukocytes (per cu mm)*	*Polymorphonuclear Cells (percent)*	*Monocytes (percent)*	*Lymphocytes (percent)*	*Eosinophils (percent)*	*Platelets (per cu mm)*	*Hematocrit (percent)*
8-23-78	18:00	5,600	85	3	11	1	110,000	28
Cimetidine therapy started, 8-23-78								
8-24-78	7:00	2,600	..	..	..	..	55,000	29
8-25-78	7:00	2,900	90	1	9	0	50,000	29
8-25-78	21:15	2,000	..	..	..	..	63,000	23
8-26-78	7:00	2,100	85	2	12	1	45,000	27
8-27-78	7:00	2,500	..	..	..	..	58,000	33
8-27-78	16:30	2,100	80	0	20	0	.....	32
8-28-78	7:00	2,500	79	0	19	2	57,000	33
8-29-78	13:30	2,500	80	5	13	2	22,000	31
8-30-78	7:00	4,300	80	5	13	2	64,000	36
Cimetidine therapy stopped, 8-30-78								
8-31-78	7:00	14,400	92	5	3	0	90,000	33
9- 1-78	7:00	10,000	91	0	9	0	110,000	31
Bone marrow aspiration, 9-1-78								
9- 2-78	15:45	11,100	91	6	3	0	160,000	23
9- 2-78	21:45	14,300	91	5	4	0	173,000	29
9- 3-78	7:00	11,700	..	..	..	..	.....	27
Cimetidine therapy started, 9-3-78								
9- 3-78	22:30	16,600	..	..	..	..	.....	29
9- 4-78	1:30	19,300	..	..	..	..	130,000	34
9- 4-78	10:15	12,100	..	..	..	..	61,000	37
9- 4-78	17:15	10,000	..	..	..	..	48,000	36
9- 4-78	21:00	8,200	..	..	..	..	40,000	35
9- 5-78	6:15	7,200	..	..	..	..	48,000	35
9- 5-78	15:15	5,900	86	3	11	0	.....	32
9- 5-78	19:30	4,700	..	..	..	..	.....	29
9- 6-78	18:15	10,200	..	..	..	..	28,000	34
9- 7-78	7:15	5,000	..	..	..	..	28,000	38
Patient died, 9-9-78								

aspiration was done. Findings included: mild hypercellularity, with mild myeloid hyperplasia with a left shift, mild normoblastic hyperplasia and an adequate number of megakaryocytes. On September 3, upper gastrointestinal hemorrhaging recurred, requiring six units of blood, and a mesocaval shunt was done. After the operation the patient was treated again with intravenous administration of 200 mg of cimetidine every six hours. The following day, platelet and leukocyte counts became depressed (Table 1). Over the next five days encephalopathy developed accompanied by deterioration of liver function test results. The patient died on September 9.

Because of the rapid shifts in the leukocyte and platelet counts, the changes are unlikely to be secondary to bone marrow suppression. The bone marrow aspiration supports this theory. The differential cell count of the bone marrow aspirate was within normal limits, and at no time during the patient's course did the peripheral leukocyte differential shift toward granulocytopenia. No plasma platelet or leukocyte antibodies were obtained. The leukopenia could be secondary to peripheral destruction, redistribution of leukocytes such as margination, or leukocyte sequestration in the body such as splenic sequestration. Possible mechanisms for the thrombocytopenia include platelet sequestration, in vivo platelet aggregation, immune-mediated platelet destruction or disseminated intravascular coagulation. In 1977 Ufberg and co-workers[1] reported a case of a patient with transient leukopenia and neutropenia appearing eight to ten days after beginning oral administration of cimetidine. The condition resolved within 10 to 12 days after stopping the drug. The bone marrow aspirate at that time showed normal cellularity. This was interpreted as being consistent with peripheral destruction of leukocytes and not compatible with bone marrow toxicity.

Except for a study by Posnett and associates[2] in 1979, no previous report of cimetidine-induced leukopenia in the literature had included a rechallenge with the drug. Neutropenia developed in their patient during a 12-day course of high-dose cimetidine (2,400 mg per day). The bone marrow showed hypocellularity compatible with toxic suppression. After a recovery period of three to four weeks, the patient was rechallenged with a standard dose (1,200 mg per day), with no apparent toxicity. They interpreted this as a dose-related, bone marrow toxic suppression. In the present case, the patient was given a second dose of cimetidine and, as with the initial cimetidine therapy, the leukocyte and platelet counts became depressed within 24 hours. This report offers additional evidence for the hematologic effects of cimetidine on the development of leukopenia and, now, thrombocytopenia. But, as previously reported, the myelotoxic potential of cimetidine was not substantiated, and new mechanisms must be considered.

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Nurse Practitioner and Physician's Assistant Clinics in Rural California

Part II: A Survey

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Twenty-six rural California clinics have employed nurse practitioners (NP's) or physician's assistants (PA's) to meet the primary health care needs of local communities. Of the 24 NP's and 5 PA's involved, 11 were men and 18 were women. Their average age was 37, and all but five were trained in California. The clinics, with less than 50 percent on-site physician supervision, averaged 19 miles in distance from the nearest physician (ranging up to 63 miles). More than half the clinics were satellites of central, physician-staffed, nonprofit clinics, a third were community-administered and two were private. Half served a whole community, a quarter were established to serve Indians and a quarter to serve Chicanos. Each NP or PA saw an average of 13 patients a day. All nonprivate clinics received subsidies from a variety of local, state and federal funds. Four of the clinics had closed or had no medical staff at the time of our survey.

NP/PA clinics are proving to be a feasible and valuable means of offering essential health care needs to remote communities.

A STUDY WAS DONE to determine the ways in which 26 rural communities in California have helped to meet their primary health care needs through clinics staffed by nurse practitioners (NP's) or physician's assistants (PA's) remote from, but supervised and supported by, physicians. While sponsorship, funding, staffing combinations and populations served varied from clinic to clinic, the use of NP's and PA's in remote communities appears feasible and acceptable.

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Part II of a two-part article. Part I appeared in the February issue.

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The first part of this study, published in the February issue of this journal, presented consumer-related, provider-related, financial or legal issues faced by these clinics. This paper describes the NP's, PA's and clinics themselves.

Methods

For survey purposes, an NP/PA clinic has been defined as one which, for more than six months, has operated four or more days a week with less than 50 percent (that is, 2½ days a week) on-site physician supervision. Survey information was gathered by telephone conversations with NP's, PA's and administrators.

Many clinics have changed their staffing pat-

TABLE 1.—*Nurse Practitioner and Physician's Assistant Clinics in Rural California (Listed North to South) by Physician Distance, Population Served and Financial Support in April 1979*

Map No.	Town (County)	Year Opened-Closed 19..	NP/PA School	Miles to Closest MD/ Sponsoring MD	Sponsor: I—Independent C—Central Clinic* H—Hospital P—Private	Predominant Population Served	Patients/ NP-PA/Day	Financial Support: Public Fee for Service: Percent Patients Medi-Cal	Financial Support: Public Fee for Service: M—Certified Medicare FP—Family Planning Contract	Financial Support: Grants, Contracts (See Code on Table 2)
1	Smith River (Del Norte)	77-	PA—Stanford	25/75	C	Indian	9	70		C,N(MD),F,I,H
2	Fort Jones (Siskiyou)	77-	NP—UC Davis	14/160	C	Indian	5	?		I
3	Doris (Siskiyou)	78-79	PA—Stanford	25/80	P	Agric.	6	5		
4	Cedarville (Modoc)	77-	NP—UC Davis	1/156	C	Agric., poor	10	30		C
5	Berber (Lassen)	78-	PA—Hawaii	19/19	H	Agric.	25	50		C,N(P)
6	Willow Creek (Humboldt)	75-	NP—UC Davis	16/16	H	Lumber	12	50		T
7	Mad River (Trinity)	78-	NP—Army	58/58	I	Lumber	9	25	M	C,N(P)
8	Covelo (Mendocino)	74-	NP—UC Davis(×2)†	47/47	I	Indian	8	?		I
9	Mendocino (Mendocino)	73-	NP—UC Davis(×2)	1/1	I	Young	14	50		T
10	Feather Falls (Butte)	77-	PA—Duke	25/25	C	Agric.	12	75	M	C,N(MD,P),F
11	Downieville (Sierra)	74-	NP—Colorado	51/51	I	Lumber	18	25	M	T,C,N(P),F
12	Lower Lake (Lake)	78-	NP—UC Davis(×2)	2/14	P	General	20	70	M	
13	Esparto (Yolo)	75-	NP—UC Davis	22/28	C	Agric., migrant	15	33	M,FP	N(MD),M,H
14	Walnut Grove (Sacramento)	73-78	NP—UC Davis	3/35	C	Migrant	10	33	FP	N(MD),M,H
15	Coleville (Reno)	78-	NP—Sonoma	32/120	C	Indian	15	60	M	N(MD),I
16	Tuolumne (Tuolumne)	77-	NP—UC San Francisco	2/10	I	Indian	12	30	M,FP	I
17	Woodlake (Tulare)	78-	NP—UC Davis	1/14	I	Chicano	20	75	M	C
18	Tule River (Tulare)	78-	NP—UC Davis	15/16	I	Indian	12	?		I
19	Porterville (Tulare)	78-79	NP—UC Davis	1/1	I	Chicano	6	?		C
20	Baker (San Bernardino)	75-77	NP—UC Davis	63/63	C	General	4	?		N(P)
21	Lucerne Valley (San Bernardino)	77-	PA—Stanford	36/36	C	Agric.	8	60	M	C,N(MD,P),F
22	San Diequito (San Diego)	77-	NP—UC San Diego	1/40	C	Agric., migrant	20	15	FP	T,N(MD),F,M,H
23	San Marcos (San Diego)	75-	NP—UC San Diego	7/23	C	Agric.	18	15	FP	T,N(MD),F,M,H
24	Santa Ysabel (San Diego)	77-	NP—UC Los Angeles	8/15	C	Agric., Indian	14	15	FP	T,N(MD),F,M,H
25	Calexico (Imperial)	78-	NP—UC San Diego	5/26	C	Chicano	15	35	M,FP	N(MD),F,M,H
26	Winterhaven (Imperial)	74-	NP—Brigham Young University	3/65	C	Retired	18	35	M	N(MD),F
	Average, (Range), or Total		NP=24; PA=5	19(1-63)/ 46(1-60)	I=8;C=14; H=2;P=2		13(4-25)	42(5-75)	M=11 FP=7	

Agric.=agricultural; UC=University of California; NP=nurse practitioner; PA=physician's assistant

*Brackets indicate satellite clinics operated by a central clinic.
†(×2) indicates that clinic is staffed by two NP's.

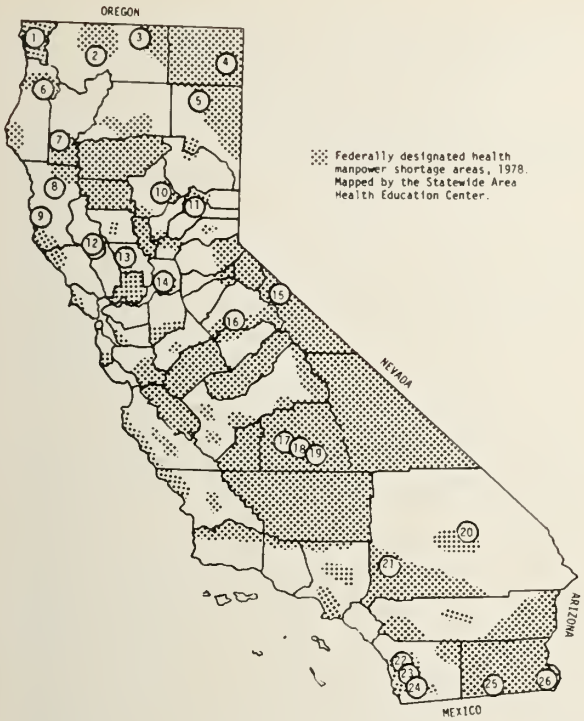

Figure 1.—Rural clinics operated by nurse practitioners or physician's assistants, March 1979. (Numbers indicate NP/PA clinic sites.)

terns and funding sources since they opened; however, this paper attempts to describe each clinic during a period it best satisfied the above definition. In most cases this was in April 1979, the time of the survey.

Results

The 26 clinics, including four which either closed or no longer use NP's or PA's, are listed in Table 1; their locations are shown on the map (Figure 1). They are scattered throughout rural California, from the Oregon to the Mexican border. Many sites had already been providing limited services before the dates listed to mark their opening as NP/PA clinics.

Twenty-four nurse practitioners and five physician's assistants staffed the 26 clinics; three of the clinics each had two NP's. All five PA's and six of the 24 NP's were men; the other 18 were women. The average age of the NP's and PA's was 37, ranging from 26 to 54 years.

The five PA's in the survey were trained as generalists, which includes care of pediatric and adult populations for preventive, acute and chronic problems. Twenty of the NP's were Family Nurse Practitioners (FNP) with similar training; the other four studied adult medicine only. The University of California, Davis, trained 14 NP's, the largest number from any one school; five others were trained outside of California.

The average distance between an NP/PA clinic and the nearest physician was 19 miles, the farthest was 63 miles. Often, official physician supervisors were not the nearest physicians, but were located at sponsoring agencies farther away. The average distance of the supervisors from the clinics was 46 miles; the greatest distance was 160 miles.

Of the clinics, 14 were outreach projects of established, nonprofit community clinics. In several instances, two or three satellite clinics were operated by a central facility (13* and 14; 20 and 21; 22, 23 and 24; 25 and 26). Eight clinics (7-9, 11, 16-19) were begun by the community which then contracted with private physicians to give supervision and part-time service. Clinics 5 and 6 were projects of community hospitals, and clinics 3 and 12 were private enterprises.

Six clinics dealt predominantly with American Indians and six with migrants or Chicanos. Three others served low income groups; of these, one dealt with all age groups, the other two served the young or retired. Fifteen clinics had been founded to serve an entire population, rather than a special target group. (This explains the overlap with the subgroup count, because most clinics serving a general population nevertheless saw a predominance of a particular group.

NP's and PA's saw an average of 13 patients a day. Clinic 6, operating at this rate, reported that it was self-supporting without grants. Clinic 12, a private practice, was solvent with 20 patients a day, while another private effort (clinic 3) failed because it never averaged more than 6 patients per day. Three clinics (5, 10, 11) projected that they would be self-supporting after start-up expenses were paid off. Clinics 7 and 18 reported below average patient figures because they were new and still building their practices. At least 13 of the clinics will not be self-supporting because they serve predominantly poor people who are not insured by public programs.

Financial support for the 26 clinics was extremely varied. The estimated percentage of patients on Medicare and Medi-Cal (California's Medicaid program) averaged 42 percent (range, 5 percent to 75 percent). Therefore, reimburse-

*Numbers in parentheses refer to clinics as designated in Table 1 and Figure 1.

TABLE 2.—*Sources of Financial Aid for NP/PA Clinics**

Code	Source	Number of Recipient Clinics (n=26)
T	County tax and/ revenue sharing	6
N(MD)	National Health Service Corps physician backup	11
N(P)	National Health Service Corps NP or PA salaries	6
F	Federal Rural Health Act	10
C	California Rural Health Act	9
M	Federal Migrant Health grants	6
I	Federal and/or California Indian contracts	6
H	Maternal and Child Health contracts	7

NP=nurse practitioner; PA=physician's assistant

*See Part I, February issue, for more detailed information.

ment of NP's and PA's by Medi-Cal is important for clinic survival. Eleven of the clinics had already been certified by Medicare for NP/PA reimbursement; many more had applied but had not yet been processed at the time of our survey.

General tax support came from the following sources: 6 clinics used county tax aid or revenue sharing funds, or both; 10 received federal health aid; 11 were given backup support by National Health Service Corps (NHSC) physicians, and six of the NP's and PA's received salaries from the NHSC. Nine clinics received some funds from the State of California Rural Health Act, including four in which the NP or PA salary was directly or indirectly paid by the state (Table 2).

Special population grants were also used. Six clinics had Federal Migrant Health grants; six had Indian contracts (federal or state); seven had Maternal and Child Health contracts, and seven had Family Planning contracts.

Most of the clinics used more than one source of support. In cases where two or three clinics were under the same sponsor, they generally, but not always, shared the same funding resources.

Four of the 26 clinics no longer use NP's or PA's. Doris (3) closed its clinic due to lack of use, but plans to start again under a different sponsorship. Walnut Grove (14) closed due to a lack of sustained leadership. Porterville's (19) NP left when his role was not accepted by the Chicano board; they are looking for a replacement. Baker (20) closed when most of the population moved away.

A brief narrative about individual clinics follows, showing some of the differences in origin, purpose, support and problems. (Numbers refer to both map and Table 1 locations.)

1. Del Norte County Indians are served by an outreach program from the United Health Service, centered in Trinidad. The PA travels to many communities throughout the county.

2. Fort Jones is also an Indian clinic. The NP there receives backup support from two NHSC physicians 13 miles away in Etna (this arrangement was to change in mid-1979), and refers patients beyond Yreka to Medford, Oregon, where service is reportedly better. The official supervisor is 160 miles away in Anderson.

3. Doris is an agricultural community with a high proportion of elderly persons. A private physician in Redding, 80 miles away, established a PA here and financially underwrote the venture, choosing not to seek government support. The PA served about six patients a day for eight months, but the clinic closed due to continued financial loss. The North-Eastern Rural Health Clinics, Inc. (centered in Westwood) planned to move two NP's (husband and wife) there in mid 1979 to be supported by a more subsidized program.

4. Cedarville clinic is also administrated by the North-Eastern Rural Health Clinics, Inc., 156 miles south, and was run by the two NP's scheduled to move to Doris. They served a lower-income population with simpler problems than the private physician practicing in the same building. Although part of a separate organization, he consulted daily. The two NP's were to be replaced by a physician.

5. Beiber is an agricultural community 19 miles from Fall River Mills where the Meyer Hospital took leadership to establish a PA. The clinic is almost self-supporting.

6. Willow Creek is a lumber community. The Humboldt Medical Center Hospital in Hoopa, 16 miles away, established the NP clinic. Though initially aided by county tax money, the clinic soon operated at a profit, partly due to good local insurance programs in the lumber industry.

7. Mad River is also a lumber community and is located 58 miles from the nearest physician. The NHSC sponsored NP was just beginning to define his role and to develop support systems at the time of our interview.

8. Covelo is the site of the Round Valley Indian Health Service, which was founded by two Indian NP's in 1974. Half of the population served is Indian and half is white. After four

years of working with part-time physician consultation, they added a full-time physician in 1978.

9. Mendocino on the coast attracts many young people who have little money. The clinic, the oldest in the survey, has been aided by a private foundation and the county health department.

10. Feather Falls is an agricultural and lumber community. An NHSC sponsored PA was established there in 1977 by the Yuba-Feather Health Center in Brownsville, 25 miles away, which has three NHSC physicians.

11. Downieville is a Sierra lumber and recreational community 51 miles from a physician. An NHSC physician was there for a year but saw few patients. He was replaced by an NP who became very active in the community, was well accepted, and soon attained a good patient flow. He is supported by a physician in Loyalton, 51 miles east, although half of the patients referred by the NP go to Grass Valley, 51 miles west.

12. Lower Lake at Clear Lake is a private venture that has had much shifting of personnel among its three sites. Two NP's are very busy at Lower Lake and are actively supported by the sponsoring private physician nearby. This was the only viable private practice clinic in the study.

13, 14. Esparto and Walnut Grove are outreach projects of the Regional Rural Health Service at Dixon, established mainly to serve migrants and the local Chicano population, although the general population increasingly has used their services. Walnut Grove, the farther of the two from Dixon, became independent in 1978. At that time, each clinic had its own NP. However, Walnut Grove closed in 1979 due to lack of sustained leadership. Dixon has two NHSC physicians.

15. Coleville is served by the Tri-County Indian Health Program, 120 miles away in Bishop, east of the Sierra Range. A third of the Coleville patients are Indian. The Bishop clinic has two full-time physicians.

16. The Tuolumne Indian Health Project serves Indians of four Sierra slope counties and its NP is backed part-time by a physician in private practice in Sonora.

17. Woodlake is the site of the United Health Organization, which serves almost exclusively Chicano families. The FNP is backed by a part-time private practitioner.

18. The Tule River Indian Health Project is a few miles east of Porterville. One NP was unable to achieve acceptance, but another (who is part Indian) has been much more successful, and is drawing Indians from as far as Bakersfield, over 50 miles away.

19. Porterville was the site of a Chicano clinic that was staffed by an NP for six months. The NP left because of role acceptance problems and the clinic is seeking alternatives in order to continue serving this population.

20, 21. Baker and Lucerne Valley are projects of the Mojave Desert Health Services in Barstow. Baker was the center of a large inter-state telephone facility and used the services of an NP for two years. However, when the telephone operation was automated, most of the population left and the clinic closed. Lucerne Valley is an agricultural community and the clinic there is stable. Another clinic is being opened in Yucca Valley by the Barstow group.

22, 23, 24. The North County Health Project (San Diego), centered in Ramona, operates several clinics. Three are staffed by full-time NP's; the others offer more limited services. The San Diequito Clinic has a family planning NP, as well as a general NP. The network has a strong communication and support system and is involved with medical education with the University of California, San Diego.

25, 26. Clinica de Salud in Brawley mainly serves migrants and the local Chicano population. It has three outreach facilities, two of which are staffed by an NP. The Winterhaven Clinic assists mostly low income, retired whites, while the Calexico Clinic serves predominantly Chicanos.

Discussion

Attempts to meet health manpower shortages have come both from rural communities taking leadership to establish their own clinics and to attract providers, and from central clinics reaching out to help outlying populations in their service area. The "community" may include all of the people or a population subgroup, usually ethnic in makeup.

Nurse practitioners and physician's assistants are becoming an increasingly acceptable answer to the need for primary care. Some NP/PA clinics have survived up to six years and have established a significant patient flow. The University of California, Davis and San Diego Family Nurse Practitioner Programs, and the Foothill College-Stanford University Primary Care Associate Program are specially geared to select and train personnel for rural areas. Foundation, federal and

state support to these schools has made this possible. The efforts of these programs are obviously effective.

The predominance of nurse practitioners over physician's assistants and of women over men in the study may break the stereotype in some minds that male PA's are the key to health care in rural areas. The 37 year average in age suggests experience and maturity, against the "fresh kid just out of school" image held by some people.

Lack of physician support has not, in most cases, been a major obstacle. Some physicians are reluctant to take responsibility for an NP or PA, especially in remote clinics; however, usually a willing physician can be found in the nearby community. And, once begun, the relationship is almost always successful. In clinics serving particular subgroups, most nearby physicians are tolerant but uninvolved; others are active in support, and only rarely is one openly hostile.

Most of the NP's and PA's feel adequately supported and, though they are nervous when beginning a satellite operation, they become confident as logistics of the clinic are developed and tested, and as their own success is recognized. It helps greatly for NP's and PA's to work directly with a physician at least once a week.

Financial support comes from patient fees, insurance and public programs. A large variety of public programs exists, which some clinics combine to form a viable budget. Often these budgets are the result of the imagination, skill and energy of the administrator (as discussed in Part I).

NP/PA clinics, simply and efficiently run, can be maintained with a patient flow of approximately 12 paying patients a day. However, when start-up costs and administrative support are included, seeing 20 patients a day is more realistic to insure that the clinic will be self-supporting. A few clinics already are achieving self-sufficiency.

Generally, patient acceptance has been good, with a few exceptions among the Indian or Chicano populations who were unable to accept a particular "Anglo" NP or PA. Three of the most successful Indian clinics are staffed by Indian NP's, and the most successful Chicano/migrant clinics are run by Chicano (or, at least, Spanish-speaking) NP's or PA's. "Anglos" have been successful in many ethnic clinics, however.

Satellite NP/PA clinics are also becoming well established, and are growing in number and impact—the result of overcoming many problems, including winning both public and professional support.

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Health Care in Modern Cuba

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An extensively organized, centrally controlled system, aimed at equalizing and improving the distribution and quality of medical services according to population and geography, characterizes the modern Cuban health care complex. Facilities of increasing sophistication are located in urban areas while an expanding series of ambulatory, multipotential polyclinics attempts to provide most health services in both urban and rural settings.

Maternal and child care, immunization programs and other forms of preventive medicine represent major priorities for expenditures. Occupational health is increasingly understood as a valuable resource, and medical professionals on all levels are being trained in significant numbers for Cuba and its allies.

MODERN CUBA is a densely populated, racially diverse island nation of 9 million people where approximately half the population is younger than 25 years old. Some 40 percent of the Cubans are white, 27 percent are black and the rest are of mixed descent.

The country has experienced many major, well-publicized political and socioeconomic changes in the last 19 years. Prominent among these have been the advances in health, education and social conditions, all of which are considered to be mutually interdependent. Even though Cuba is still a developing country, the government has invested heavily in the medical system in an attempt to mold a strong, productive and grateful citizenry. The planning has been geared to provide effective, accessible health care to both urban and rural areas.

The information contained in this report is derived from a review of available literature about medical services in Cuba. The authors also participated in a two-week trip to Cuba, organized by the American Medical Student Association (AMSA), the purpose of which was to observe the organization and evaluate the goals of the Cuban health care system.

Background

Before Fidel Castro's revolutionary government assumed control in 1959, Cuban health care was delivered by a variety of disparate systems. The government maintained facilities for the care of tuberculosis, leprosy and syphilis as well as hospitals for the poor; provided some maternal and child care, and dealt with public health problems. The military had its own hospitals as did larger

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companies and a few religious groups. A series of "mutualistas," an early form of health maintenance organization, were also becoming an increasingly successful enterprise. Havana, the capital, with 22 percent of the population, supported 65 percent of the physicians.[1]

The Present Health Care Structure

The present system has shifted control away from the private sector. All services, training, public health and epidemiology are now centrally directed by the Ministry of Public Health (MINSAP). The goal has been to establish a set of uniform national objectives and standards for health care, and to try to implement these services as equally as possible in all parts of the island. A belief in the ultimate value of primary care and preventive medicine has helped to shape the structure and function of the Ministry.

Figure 1.—Most children in Cuba are members of organized youth groups. These boys belong to the Pioneers, a group that monitors and controls the ballot boxes on election day. (Photograph: E. Janoff)

Figure 2.—A billboard sponsored by a Committee for the Defense of the Revolution (CDR) in Havana. In the absence of free enterprise and, therefore, advertising, most graphic designs are political. (Photograph: M. Boehnert)

There are four levels of care available. The National Institutes carry out highly specialized procedures, such as kidney transplants and some heart operations, and conduct research. Provincial hospitals provide subspecialized tertiary care. Regional and municipal facilities offer secondary specialty care (such as most general surgical operations). Each level has a corresponding administrative and statistical counterpart. The national system of statistical monitoring is also very important in the formation and evaluation of the health program.

At the very core of the Cuban health care system is the fourth level or basic functional units—the polyclinics. These offer outpatient services to 25,000 to 30,000 people within a designated geographic area. The health team approach uses doctors, nurses, psychologists and a broad assortment of technicians. There is a continuing debate about what kinds of doctors should provide first-contact care, but the present system offers specialists in internal medicine, pediatrics, obstetrics-gynecology and dentistry. General practitioners are more often found in rural areas. A family file, with individual records included, is maintained to promote integrated, continuous care. The polyclinics have radiographic equipment, laboratory and some counseling services available.

The preventive medicine programs are centered around the polyclinic. Community involvement is crucial to the success of these programs. All aspects of Cuban life are highly organized—most children, for example are members of organized youth groups (Figure 1)—and this extends down to the level of residential blocks which are represented by the Committees for the Defense of the Revolution (CDR). The CDR's began in 1960 as local mechanisms to suppress counterrevolutionary activity (Figure 2). Since then, their role has expanded and they now also seek to improve interaction among parents, children, school, work, the health care system and the government. The representatives on CDR's are people elected locally whose duties now include such things as making

sure women go for prenatal visits and Papanicolaou tests, soliciting blood donations and promoting mass immunization programs. In exchange for these services, the polyclinic staff gives lectures concerning common problems of women and children and about prevalent diseases, sanitation and environmental hazards.

Polyclinic administrators meet monthly with CDR members, representatives of factories in the area served and with other public groups such as the labor unions, the Federation of Cuban Women (FMC) and the Young Communists League (UJC) to discuss any problems with the services. Such problems may include long waiting times, discontinuity of doctor-patient relationships and equipment shortages. Public opinion carries so much influence that medical personnel often find their decisions preempted by popular concerns. In fact, national, provincial and area health commissions, which are responsible for planning the goals and priorities of the Ministry of Health, all have representatives from these mass organizations.[2]

Although the number of hospital beds has increased since 1959, the total number of hospitals has declined because MINSAP has centralized hospital facilities while decentralizing ambulatory care. Rural hospitals and polyclinics, on the other hand, have increased dramatically in quantity. The attempt has been made to balance rural and urban availability, to stress prevention over cure and to substantially increase the number of health care professionals.

Medical Education and Health Manpower

Premedical education in Cuba consists of seven years of primary school, three years of secondary education and three years of baccalaureate studies. Admission to medical school is competitive, with acceptance based on academic records in math and sciences, political orientation and a history of volunteer work in public service. The government limits the number of medical students to 20 percent of university enrollment. In recent years roughly 50 percent of first year medical students have been women.

The medical school curriculum consists of two years of basic sciences, two years of clinical sciences, one year of clinical externships and one year of rotating internship. During the first two years of basic sciences other subjects are studied, including history, Marxism, physical education, economy and medical ethics. In addition, one day a week is spent working in a polyclinic and one month a year is devoted to labor in the sugar cane fields or in a polyclinic. Medical research is conducted at several research institutes and is not interrelated with the medical education system as is the case in the United States.

The Hippocratic oath is no longer used in Cuba. Instead medical graduates take an oath that calls for the following: (1) renunciation of private practice and agreement to serve in a rural area; (2) repaying the people, through service, for the opportunity of gaining a medical education; (3) promotion of preventive medicine and human welfare; (4) continuous striving for scientific excellence and political devotion; (5) proletarian internationalism, and (6) defense of the Cuban Revolution.[3(p45)]

Three years of service in a rural area are required of all medical school graduates, after which residency training in 38 specialties is available. Estimates of the number of physicians entering specialty training after rural service vary from 30 percent to 80 percent.[4(p417),5(p846)] The number of residency positions available in each specialty is controlled by the Ministry of Health according to the needs of the health system. At present there is not a specialty of family practice in Cuba.

Most Cuban medical students accept without complaint the aspects of their educational system that many in the United States would find oppressive. Productive physical labor is accepted as an important part of their education; mandatory rural service and controls on the numbers of residencies are seen as necessary to meet the needs of the people. The concept of charging patients to see physicians is viewed as totally foreign. On the other hand, no tuition is charged to obtain a medical education and many students are paid an allowance while in school, according to need.

Continuing medical education (CME) is primarily the responsibility of the National Center for Information on Medical Sciences (CNICM) which publishes, for a number of specialty fields, review journals containing abstracts of articles from journals from around the world. The CNICM also publishes journals containing original articles by Cuban investigators, maintains a national system of medical libraries, collects information on specific problems in response to requests from individual physicians and issues booklets on topics of special interest.[3(p60)] In addition, several seminars on current medical advances are held continuously throughout Cuba, and all physicians are

Figure 3.—In the major obstetric hospital in Havana, as in most hospitals, newborns are returned to their mothers within four to six hours. (Photograph: M. Boehnert)

required to visit Havana periodically for CME courses.

Before the revolution there were approximately 6,300 physicians in Cuba, 65 percent of whom were located in Havana.[3(p51)] It is estimated that in the first few years after the revolution at least 33 percent of all physicians left the island. However, the departure of doctors did not begin with the revolution. Up to 14 percent of medical graduates left the country each year for the United States or elsewhere, but the process accelerated considerably soon after the revolution.[3(p51)] Rapid steps were taken by the government to increase the number of physicians so that by 1970 some 5,600 new doctors had been trained. By 1968 there were 7,500 physicians in Cuba, 40 percent of whom were located in Havana. At present, more than 1,000 physicians graduate each year. Besides meeting its own health manpower needs, Cuba supplies doctors to assist 18 other socialist countries.

As of 1971 there were approximately 200 physicians in full-time and 700 in part-time private practice while being employed part time by the government.[3(p53)] Since 1965 medical school graduates, as has been mentioned, have renounced private practice as part of their oath. Physicians who were in private practice before that time have been allowed to remain so if they desire. As an incentive to work for the government health service, private physicians have been offered salaries higher than the average. Currently, physicians in their first year of practice earn 250 pesos a month and physicians who are at the highest level of specialty training and status earn 750 pesos a month. The average Cuban worker earns 150 pesos a month.

Maternal and Child Health

Maternal and child care has assumed the highest priority and, therefore, is allotted the most funds in order to assure the highest possible number of healthy children. This priority also reflects an increased emphasis on the equality of women, as documented by law and equal wages.

Breast cancer is a leading cause of female mortality and radical mastectomies are the most common treatment. Breast self-examination, however, is not taught. Cuban physicians would prefer to do Papanicolaou tests for cervical cancer on a yearly basis; at present, however, they are done biannually to insure availability to all women.

There is no defined national policy on population control and all contraceptives are available to women over the age of 15; intrauterine devices are the most popular form. Abortions are generally available in the first trimester to prevent the morbidity associated with illegal procedures, although this service is not offered at every hospital.

Prenatal care is strongly emphasized. Classes are given, usually through the local polyclinic, on nutrition, birth techniques, exercises and psychoprophylaxis. Mothers attend an average of nine prenatal visits per pregnancy. Amniocentesis is being used with increasing frequency. In outlying areas, these services are being carried out by rural hospitals and "hogares maternos," a type of home clinic where high-risk mothers may spend up to several months before labor.

Nationally, more than 97 percent of all children are delivered in hospitals.[6] Cuban physicians discount the value of home deliveries because of the expense, lower quality of available neonatal care and the problems posed for public health.

Women are encouraged to remain active during their labor if possible and often rocking chairs are provided. Little fetal monitoring equipment is available. Episiotomies are done with administration of a local anesthetic for most first births; general anesthesia is not used routinely. Cesarean sections are carried out in 7 percent of first deliveries, with an overall average of 14 percent. Forceps are used in 5 percent of cases. Infant mortality was recorded to be 26.1 per 1,000 live births in 1974 as compared with 18.5 in the United States and 81.6 in Guatemala.[7(p691)]

Newborns are returned to their mothers within

four to six hours of birth (Figure 3) with a card showing what inoculations will be required and when. Most children are breast-fed and all mothers contribute to a milk bank. The average hospital stay is five days postpartum. There is no out-of-pocket expense to patients or their families.

Diabetes is a special problem in Cuba and is one of the main areas of clinical research. Programs are available for mothers and children at high risk for this disorder.

Women are given 12 half-days off during pregnancy for medical attention. They have 6 weeks off before the birth and 12 weeks after, all with pay. Day care centers are available because many women work, although there is a shortage of such facilities.

Many women who served as village midwives in the past have been given additional medical training and are now incorporated into the health care team. Nurses can specialize in obstetrics with two years of additional training, and in neonatology, anesthesiology or intensive care, with one year of further training.

Psychiatric Care

Treatment of psychotic patients in Cuba consists of inpatient care, occupational therapy and, when possible, helping patients to return to independent lives. This process involves the following stages: (1) total hospital confinement, (2) weekend trips outside the hospital on a pass, (3) working outside the hospital but returning to sleep at night, (4) moving to a halfway house with periodic hospital visits and, finally, (5) discharge with follow-up visits at a polyclinic. There are several psychiatric hospitals in Cuba, the largest is in Havana and houses 2,500 patients. A team approach to therapy is used involving psychologists, sociologists, nurses and psychiatrists.

Neuroses, depression and personality disorders are treated as outpatient problems and are handled at polyclinics and municipal hospitals. Nearly identical pharmaceutical agents are used in Cuba as in the United States, except that all medications are ordered by generic name. Electroconvulsive therapy is used for the same indications as in this country.

As part of the national plan to combat mental disorders the Cuban government conducts periodic public education campaigns on mental illness. As part of this campaign, a yearly sports competition is held for mental patients. Before these events, psychiatric patients carry Olympic-like torches through the countryside, stopping at towns they pass through to give talks on mental illness. This is an attempt to destroy the many myths concerning mental illness and to foster understanding and acceptance of psychiatric treatment among the people.

Occupational Health

Occupational safety and health is another area receiving a high priority from the Cuban Ministry of Health. Occupational health services and facilities are integrated into the general health care system with polyclinics serving as the centers of supervision.

Full-time technicians, with training in occupational safety and health, work in the polyclinics and are responsible for the safety and health of factory workers in their health areas. Regular inspections are made (every three months in hazardous work places) and periodic general checkups are provided to the workers. Employees at factories without onsite medical facilities are taken to their area polyclinic for any medical problems that arise while on the job. Some of the larger factories have health facilities staffed by nurses or, less often, by a physician.

A second major component of safety surveillance is provided by the members of the work place safety and hygiene committee. This is one of 13 committees at each work place responsible for various aspects of worker activity. Members of the safety committee are responsible for maintaining safety standards, insuring that workers receive periodic checkups and needed immunizations, and meeting with other safety committees to discuss ideas and to provide information for higher levels of decision making.

At the national level, occupational safety and health standards are set within the Ministry of Health, and a national institute conducts research on occupational and environmental health hazards. Occupational health is a specialty requiring residency training and, similar to the situation in the United States, few physicians are practicing in this field at present.

Cubans work eight hours a day and have a month of vacation per year. There is no unemployment.[4(p403)] As mentioned earlier, generous leave is provided for women workers during and after pregnancy. It is not uncommon for work places to have full-time readers who read from

newspapers and other publications, chosen by the workers, over microphones.

Statistics

To understand the status of health care in Cuba it is important to look at how the organization of the health care system and development of health care resources have resulted in improved health for the Cuban population.

During the past decade in Cuba, poliomyelitis, diphtheria and malaria have been eradicated.[8,9] There has been a substantial reduction in the incidence of infectious diarrhea (the mortality being an eighth in 1975 of what it was in 1962[10]), as well as of tetanus, tuberculosis and all waterborne diseases. The mortality for pertussis is the second lowest in the western hemisphere and, for tetanus, the third lowest.[9(pp20,21)] Occurrences of chicken pox, measles, mumps, typhoid and infectious hepatitis have been irregular. There still remains a problem with certain parasitic infections.[8] Table 1 compares the incidence rates of a few diseases in Cuba with those in certain other countries in the western hemisphere. It can be seen that while Cuba is considered an underdeveloped country economically, it compares favorably with developed nations in certain health statistics.

The average Cuban visits a physician 4.1 times per year and a dentist 0.7 times a year.[10] Approximately 98 percent of deliveries occur in hospitals, and 60 percent of the population has running water, compared with 68 percent in Argentina and 38 percent in Bolivia.[9(p64)] While one might suspect that improved health statistics in Cuba are due to underreporting, the reverse appears to be the case. Along with increased emphasis on delivery of health services has come an increase in the reporting of health information. This is evidenced by the fact that in 1956, 53 percent of deaths were certified by physicians compared with 98 percent in 1967.[3(p66)]

The incidence of gonococcal infections, for example, is (see Table 1) 469.3 in the United States versus 47.0 per 100,000 in Cuba in 1975. These figures are accepted by the Pan American Health Organization. There appears to be easy and acceptable access to health care, especially in urban areas where gonorrhea most likely will be found. However, we observed no major emphasis on sex education and official representatives tended to deny that social problems such as alcoholism, child abuse and prostitution are still major concerns. Although social responsibility and peer pressure are significant external influences in Cuba, we are not in the position to comment on whether a major difference in social mores is responsible for this statistical gap or whether such a gap does indeed exist.

Infant mortality has decreased from 37.6 per 1,000 live births in 1964 to 26.1 in 1974.[8] The mortality among preschoolers (children 1 to 4 years of age) was cut in half between 1962 and

TABLE 1.—*Incidence* of Select Diseases in Five Countries in the Americas for 1975†*

	Tuberculosis	*Syphilis*	*Gonococcal Infections*	*Poliomyelitis*	*Measles*	*Diphtheria*	*Typhoid Fever*
Argentina	58.5	45.0	50.2	0.0	103.2	1.0	5.6
Bolivia	176.0	42.8	31.6	0.5	68.1	4.0	13.8
Cuba	14.2	47.6	47.0	0.0	115.4	0.0	4.1
Guatemala	104.2	14.6	45.2	0.7	25.1	0.3	17.1
United States	16.0	37.7	469.3	0.0	12.6	0.1	0.2

*Rates per 100,000 population.
†From Pan American Health Organization.[9]

TABLE 2.—*Five Leading Causes of Death in Children by Age, 1973**

1-4 Years	*Rate (per 100,000)*	*5-14 Years*	*Rate (per 100,000)*
Influenza, pneumonia	19.7	Accidents	12.3
Accidents	18.6	Malignant tumors	6.7
Congenital anomalies	13.2	Congenital anomalies	3.2
Malignant tumors	10.1	Influenza, pneumonia	2.3
Diarrheal diseases	6.3	Heart disease	1.6
Other	52.1	Other	18.9
TOTAL	120.0	TOTAL	26.1

*Adapted from Corteguera et al.[8]

TABLE 3.—*Principal Causes of Death in Cuba, 1975**

Condition	*Rate (per 100,000)*
Heart disease	148.3
Cancer	98.2
Cardiovascular accident	50.5
Influenza, pneumonia	40.5
Accidents	32.7

*From Ministry of Health of Cuba.[10]

1973 (from 2.1 deaths per 1,000 to 1.2).[8] Table 2 illustrates the five leading causes of death in children in Cuba in 1973 and Table 3 lists the principal causes of death throughout the population in Cuba in 1975.

Conclusion

The statistics in Tables 1 through 3 point out the remarkable progress made by the Cuban health system during the past 20 years. This progress is all the more remarkable when one considers the past loss of large numbers of health professionals, and the continuing economic embargo by the United States that contributes to shortages of medicine and technology. The guiding philosophy of the Cuban government and most health professionals, which has been the driving force behind these gains, is best stated by Milton Roemer:

> The rationality of the entire Cuban approach, in accordance with the needs of the people rather than the personal convenience or wishes of the health professions, is its most important characteristics."[3(p77)]

Yet, statistics also point out what Cuban physicians and other health workers readily admit, that there is much left to be done.

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Salvaging a Severed Member?

WHAT MUST YOU TELL any lay organization that you have opportunity to talk to about helping to salvage a severed part of the body? You remove whatever gross dirt there is. You then place that amputated part in a plastic bag, squeeze the air out, seal it with a rubber band, and place the plastic bag in a chest that you've put ice cubes in (preferably with a little bit of water with the ice cubes). Then you have probably bought hours of time because that part now has the metabolic rate lowered and you can replant it at a much later date.

—HAROLD E. KLEINERT, MD, *Louisville, Kentucky*

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Refer to: Roberts NK, Child JS, Cabeen WR Jr: Cardiomegaly and cyanosis on exercise—The diagnosis of Ebstein anomaly (Clinical Notes in Diagnostic Cardiology). West J Med 132:272-275, Mar 1980

Cardiomegaly and Cyanosis on Exercise

The Diagnosis of Ebstein Anomaly

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PAUL WOOD wrote in his classic text, "I have personally catheterized seven cases of Ebstein's disease, but do not propose to catheterize another wittingly!"[1] This comment reflects Dr. Wood's experience with lethal tachyarrhythmias while evaluating these patients. Now, fortunately, we not only are able to deal effectively with the high frequency of arrhythmias in this situation but we also have noninvasive methods for making the diagnosis. A case is presented to illustrate a clinical condition in which Ebstein anomaly should be considered and the diagnostic techniques used.

Report of a Case

A 35-year-old woman was known to have heart disease since infancy. From the age of 31 she began to experience shortness of breath on exercise and cyanosis developed. She noted that she had palpitations but claimed that they were of short duration. She also had some atypical chest pain which did not radiate significantly and which she could not relate to rest or exercise.

Examination at rest showed no cyanosis or clubbing of the fingers or toes. The jugular venous pressure and the arterial pulses were within normal range. Auscultation disclosed a rather widely split and clicking first sound. The second sound was also widely split. A harsh holosystolic murmur was heard down the left sternal border. No third or fourth sounds could be heard.

A radiograph of the chest (Figure 1) showed slightly increased pulmonary vascularity and a rather full cardiac shadow. There was a right atrial prominence and a rather slender vascular pedicle. Electrocardiographic findings (Figure 1) showed a normal PR interval and a conduction delay over the right ventricle and a low QRS voltage over the precordium.

An echocardiographic study disclosed a relatively normal tricuspid valve except for systolic hammocking. There was a 60-msec delay in tricuspid valve closure as compared with the mitral valve closure (Figure 2).

A cardiac catheterization was carried out to confirm the clinical suspicion of Ebstein anomaly. There was a step-up in oxygen saturation from 50 percent in the superior vena cava to 64 percent in the right ventricle and pulmonary artery. Calculations based on these data showed that the pulmonary to systemic flow ratio was 1.5:1. Pressure measurements and intracardiac electrograms were recorded simultaneously on withdrawal of a Zucker catheter from the right ventricular outflow tract to the right atrium (Figure 3). In the body of the right ventricle a typical ventricular pressure trace was obtained as was a right ventricular electrogram (Figure 4A). On withdrawal, an atrial pressure trace was obtained but the simultaneous electrical recording was of a ventricular chamber (Figure 4A). This represents the atrialized portion of the right ventricle. Withdrawal of the catheter across the atrioventricular ring achieved a simultaneous atrial pressure and atrial electrogram (Figure 4B). A further electrical study was carried out in which the pressure measurements were again obtained, but this time the Zucker catheter was used as a pacing electrode (Figure 4C,D) When the catheter was in the body of the right ventricle, a typical pressure trace was obtained and the right ventricle was paced. Withdrawal of the catheter to the atrialized portion of the ventricle caused an atrial trace but still the ventricle was paced (Figure 4C). Further withdrawal across the atrioventricular ring achieved a simultaneous right atrial pressure and pacing trace (Figure 4D). The Zucker catheter was then used

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*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Padget disease. An explanation may be found on page 78 of the July 1978 issue.

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as a hydrogen electrode and disclosed a left-to-right shunt at atrial level. Cineangiograms were recorded in the right ventricle and right atrium (Figure 3A). The ventricular injection of contrast medium showed the displaced tricuspid valve leaflets and the moderately severe tricuspid regurgitation. Between the working right ventricular cavity and the atrioventricular ring, there was a large atrialized portion of the right ventricle.

Discussion

It is a good clinical rule of thumb[2] to consider the diagnosis of Ebstein anomaly of the tricuspid valve as a probability in children with cyanosis who experience recurrent episodes of paroxysmal tachycardia; however, cyanosis does not always develop in patients with this condition. Indeed, although our patient had a rather severe anatomic form of the anomaly she was not cyanotic. Despite the moderate tricuspid regurgitation, the large size of the right atrium prevented significant elevation in right atrial mean pressure and allowed the existence of a significant left-to-right shunt through the widely patent foramen ovale. A pronounced displacement of the tricuspid valve into the right ventricle, resulting in a small right ventricular cavity and right ventricular dysfunction may cause elevation of the right atrial pressure. This elevation,

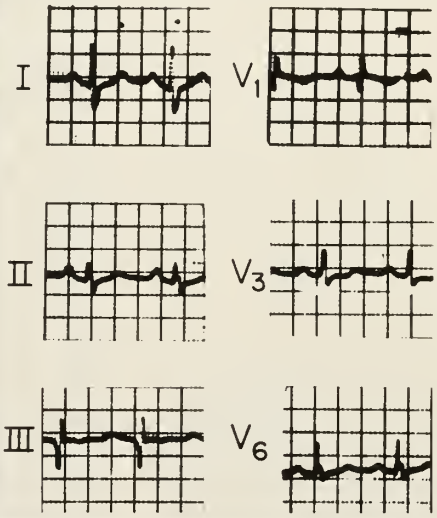

Figure 1.—A radiograph of the chest and electrocardiographic studies. The radiograph shows an enlarged heart, particularly the right atrium and ventricular shadow. The lung fields show a slight increase in vascularity. The electrocardiographic findings show a normal PR interval and low-voltage QRS complexes.

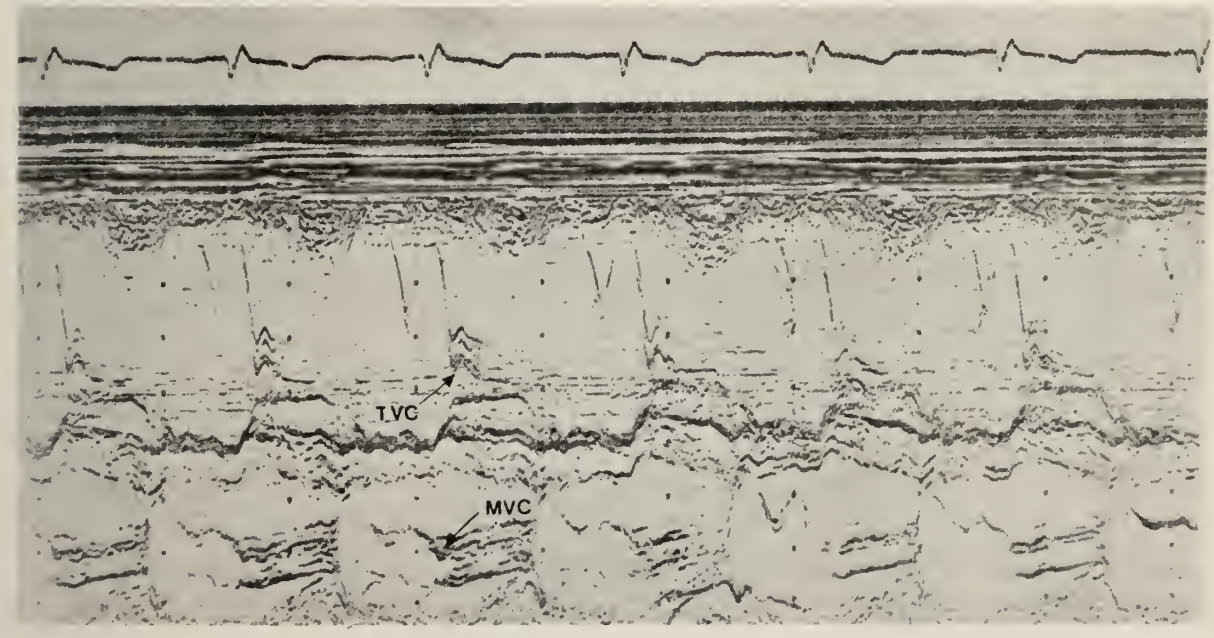

Figure 2.—An unretouched echocardiogram shows tricuspid valve closure (TVC) and mitral valve closure (MVC). The MVC is 60 msec ahead of TVC.

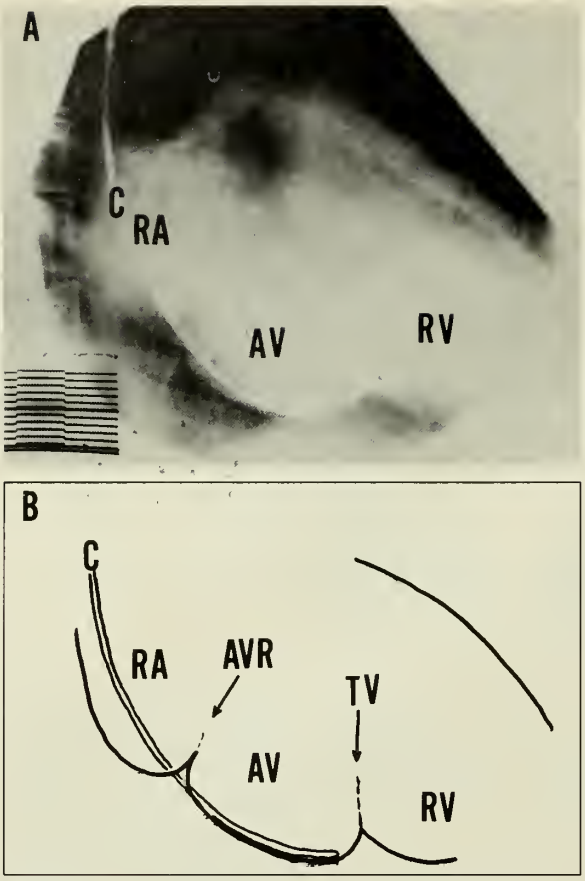

Figure 3.—**A,** A right ventricular angiogram shows right ventricle (RV), the atrialized portion of the right ventricle (AV) and the right atrium (RA). The catheter (C) is at the junction of the AV and RV. **B,** A diagram of the RA, AV and RV, noting the position of the atrioventricular ring (AVR) and the tricuspid valve (TV).

in turn, may reverse the normal relationship between left and right atrial pressures and, where there is an open foramen ovale, may allow a right-to-left shunt to develop. Ventricular dysfunction may be secondary to persistent atrial or ventricular arrhythmias, pulmonary stenosis or pulmonary hypertension. About 50 percent to 80 percent of patients with Ebstein anomaly at some point have cyanosis.[2]

Auscultation of the precordium in Ebstein anomaly frequently discloses a rather characteristic component to the first sound, namely the "sail" sound.[3] This sound coincides with the abnormal movement of the large, mobile anterior leaflet of the tricuspid valve. Depending on the amount of downward displacement of the tricuspid valve there may or may not be a murmur of the tricuspid insufficiency.

A third of patients with Ebstein anomaly have a prolonged PR interval and a third have a preexcitation syndrome of the Wolff-Parkinson-White type B variety.[4] Patients with a preexcitation syndrome may frequently have episodes of tachycardias and even if the 12-lead electrocardiogram does not support the pressure of accessory pathways, the patient may still suffer from significant tachycardias. An electrocardiogram, as was the case with our patient, generally shows right atrial enlargement and low-voltage QRS complexes across the precordium.

Chest x-ray studies may be quite typical and

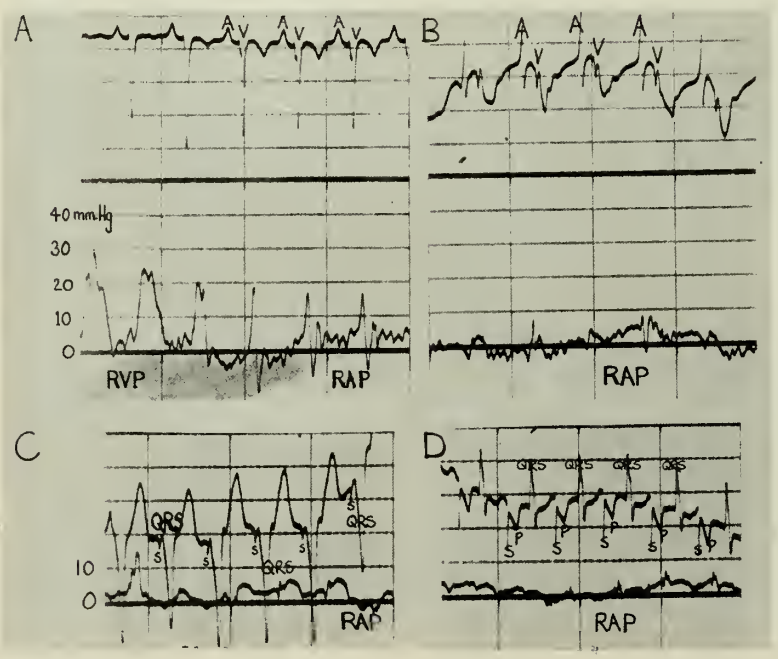

Figure 4.—Selected tracings from the electrophysiologic study: **A,** A typical ventricular electrogram showing atrial (A) and ventricular (V) activity. The pressure on the left is right ventricular (RVP) and on the right, atrial (RAP). **B,** A typical atrial electrogram showing very prominent A waves and small V waves; the simultaneously recorded pressure below is atrial. **C,** An electrogram showing a pacing stimulus (S) and typically aberrated beat of right ventricular pacing (QRS). The simultaneous pressure trace below is RAP and is, therefore, indicative of an atrialized pattern of the right ventricle. **D,** An electrographic study showing S followed by an atrial complex (P) and a normal QRS complex. The simultaneous pressure trace is RAP.

show a large right atrium, narrow vascular pedicle and pulmonary oligema. In the most severe variants of Ebstein anomaly there is a rather large atrialized portion of the right ventricle which gives the characteristically rounded right atrial shadow. A normal cardiac silhouette is compatible with the milder variants.

Although chest x-ray and electrocardiographic findings may be indicative of the Ebstein anomaly, echocardiography is the noninvasive test that is likely to give the most reliable results. The typical M-mode finding is that the mitral valve closure precedes the tricuspid valve closure by more than 50 msec (Figure 2).[5] Abnormal septal motion (due to right ventricular volume overload), increased tricuspid valve motion and decreased diastolic closure velocity of the tricuspid valve may also be seen.[6] Patients with mild forms of the anomaly may have a normal valve. To obtain accurate results the tricuspid valve should be imaged in the same plane as the mitral valve.[7] Two-dimensional, real-time echocardiography may, however, become more important as both the shape and insertion of the tricuspid valve can be visualized.[8]

At cardiac catheterization one generally finds that there is an open foramen ovale. As the mean left atrial pressure is normally higher than the right atrial pressure, the net shunt is from the left to right. The electrode catheter with a lumen for pressure measurements should be advanced from the superior vena cava because if they are advanced via the inferior vena cava they may miss the larger part of the atrialized portion of the right ventricle.

The three major tests that are carried out using the electrode catheters are: (1) hydrogen electrode study, (2) simultaneous recording of pressures and intracardiac electrograms and (3) simultaneous recording of pressures and intracardiac pacing.

An intracavity electrogram is recorded via the electrode catheter which is sequentially placed in the pulmonary artery, right ventricle, right atrium and vena cavae. The patient then takes a deep breath of hydrogen and the hydrogen dissolves in the blood. In the case of a left-to-right shunting atrial septal defect there is an early appearance time of the hydrogen at right ventricular and pulmonary artery level but not at the vena cavae. The appearance time is noted from the time of the hydrogen inhalation to the time that the baseline of the intracavity electrocardiogram shifts. As Figure 4 illustrates, it is possible to show an area of atrialized ventricle by either recording a ventricular electrogram or by pacing the ventricle and simultaneously recording an atrial pressure. Both of these methods are most accurate in the severest form of the anomaly and least accurate in the mildest form.

Finally, the disclosure of a discrepancy on angiographic studies between the atrioventricular ring and displaced tricuspid valve should confirm the diagnosis.

In summary, the diagnosis of Ebstein anomaly may be suggested by the history of cyanosis on exercise, mild clubbing of the fingers in a patient who is not cyanotic at rest, or cyanosis during attacks of supraventricular tachycardia. Supraventricular arrhythmias, in a patient who has a large right atrium and low, widened QRS complexes may justifiably raise the suspicion of Ebstein anomaly. Evidence of a type B Wolff-Parkinson-White syndrome on the electrocardiogram, in combination with any of the findings above, should change a possible suspicion to a probabiliy.

Currently, in the diagnostic armamentarium we have both noninvasive and invasive techniques. The echocardiogram is proving to be a useful tool and the electrode catheter, either as a recording electrode or as a pacing electrode acting simultaneously with pressure measurements, is a valuable diagnostic aid when used in conjunction with findings from a right atrial and right ventricular angiogram.

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ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles they consider to be important in other journals. These titles together with a brief assessment of the articles are published for the information of our readers.*

Estrogen Replacement Therapy I: A 10-Year Prospective Study in the Relationship to Osteoporosis

Nachtigall LE, Nachtigall RH, Nachtigall RD, et al

Obstetrics & Gynecology
53:277-281, Mar 1979

DISCIPLINES: General and Family Practice, Surgery, Obstetrics, Gynecology, Orthopedics

READABILITY: Very good

A ten-year prospective study is reported on the effects of estrogen on the prevention of osteoporosis. It was prompted by the observation that by age 60 there are ten times as many forearm fractures among women than among men, that one of four white women over 60 have spinal compression fractures, and that one woman of five with hip fractures will die within three months of the injury. Early use of estrogen in postmenopausal women prevented or halted the osteoporosis process.

Fetal Cranial Injuries Related to Delivery With the Malmström Vacuum Extractor

Plauché, WC

Obstetrics & Gynecology
53:750-757, Jun 1979

DISCIPLINES: General and Family Practice, Obstetrics, Pediatrics

READABILITY: Excellent

This article is written without bias. It tells of the uses as well as the limitations of vacuum extractors. Techniques to be followed to reduce the recurrence of scalp laceration and subgaleal hematomata are described. The article should be required reading for anyone interested in vacuum extraction, and it contains an excellent bibliography.

Morbidity and Mortality of Advanced Gestational Age: Post-Term or Postmature

Callenbach JC, Hall RT

Obstetrics & Gynecology
53:721-723, Jun 1979

DISCIPLINES: General and Family Practice, Obstetrics, Pediatrics

READABILITY: Excellent

Postmaturity of infants, as compared with prematurity, has received relatively little attention. But these authors point out that even large, appropriately grown, postterm infants are at risk of anoxic encephalopathy, aspiration pneumonia and intracranial hemorrhage. The authors hypothesize that "the senile placenta has enough reserve to provide for the continued growth of the fetus but not for the stress of labor."

Adolescent Contraceptive Use: Current Status of Practice and Research (Reviews)

Freeman EW, Rickels K

Obstetrics & Gynecology
53:388-394, Mar 1979

DISCIPLINES: General and Family Practice, Obstetrics, Gynecology, Psychiatry

READABILITY: Very good

This review makes several points regarding adolescent pregnancies: (1) 55 percent of unmarried women have intercourse by age 19. (2) Only a small percentage (16 percent) of sexually active teenagers desire pregnancy. (3) Lowering of the rate of teenage pregnancies and abortions can be achieved only when adolescents have full knowledge of and free access to confidential contraceptive service. (4) There is no evidence that the availability of contraceptives encourages premarital sex.

Female Sterilization and Subsequent Ectopic Pregnancy

Wolf GC, Thompson NJ

Obstetrics & Gynecology
55:17-19, Jan 1980

DISCIPLINES: Obstetrics, Gynecology, General and Family Practice, General Surgery

READABILITY: Very good

In one of 13 ectopic pregnancies there had been a tubal sterilization procedure. That finding came from an eight-year retrospective study. The sterilization can actually be a causative factor. Past history of a tubal ligation should remind us to include ectopic pregnancy in our differential diagnosis.

Fetal-Maternal Bleeding Associated With Genetic Amniocentesis

Mennuti MT, Brummond W, Crombleholme WR, et al

Obstetrics & Gynecology
55:48-54, Jan 1980

DISCIPLINES: Obstetrics, Gynecology, Radiology, Ultrasound

READABILITY: Very good

These authors present evidence to show that fetal-maternal (fetal-to-maternal) bleeding does occur as a result of amniocentesis. This added hazard reenforces the dictum that placental localization must precede amniocentesis. In addition, they recommend that Rh immunoglobulin be administered to all Rh negative nonsensitized women after amniocentesis.

—E. R. W. FOX, MD
Coeur d'Alene, ID

in memoriam

California Medical Association

Arnov, Boris, Los Angeles. Died April 2, 1979 of multiple myeloma, aged 86. Graduate of St. Louis University School of Medicine, 1926. Licensed in California in 1926. Dr. Arnov was a member of the Los Angeles County Medical Association.

Baron, Shirley H., San Francisco. Died December 19, 1979 in San Francisco, aged 75. Graduate of Cornell University Medical College, New York, 1927. Licensed in California in 1927. Dr. Baron was a member of the San Francisco Medical Society.

Bateman, Alfred V., Escondido. Died August 18, 1979 of heart disease, aged 59. Graduate of the University of Oregon Medical School, Portland, 1945. Licensed in California in 1948. Dr. Bateman was a member of the San Diego County Medical Society.

Bowles, A. Morse, Santa Rosa. Died December 10, 1979 in Santa Rosa, aged 83. Graduate of the University of California Medical School, Berkeley-San Francisco, 1925. Licensed in California in 1925. Dr. Bowles was a retired member of the Sonoma County Medical Association.

Clark, Dana Vinyard, San Francisco. Died in January 1980 in San Francisco, aged 84. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1923. Licensed in California in 1931. Dr. Clark was a retired member of the San Francisco Medical Society.

Coaker, William J., San Jose. Died January 7, 1980 in Willow Glen, aged 47. Graduate of Loyola University of Chicago, Stritch School of Medicine, Chicago, 1956. Licensed in California in 1962. Dr. Coaker was a member of the Santa Clara County Medical Society.

Easter, William A'Dolph, Joshua Tree. Died November 19, 1979 in Loma Linda, aged 76. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1934. Licensed in California in 1934. MD degree from California College of Medicine, 1962. Dr. Easter was a retired member of the San Bernardino County Medical Society.

Garrard, William F., San Francisco. Died January 13, 1980 in Willits, aged 35. Graduate of the Medical College of Georgia, Augusta, 1972. Licensed in California in 1973. Dr. Garrard was a member of the San Francisco Medical Society.

Greenson, Ralph R., Los Angeles. Died November 24, 1979 in Santa Monica of heart disease, aged 68. Graduate of Universität Bern, Medizinische Fakultät, 1934. Licensed in California in 1935. Dr. Greenson was a member of the Los Angeles County Medical Association.

Holbert, Duncan A., Santa Cruz. Died November 28, 1979 in Santa Cruz, aged 63. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in California in 1944. Dr. Holbert was a member of the Santa Cruz County Medical Society.

Hough, Victor H., Bishop. Died September 30, 1978 of cerebrovascular accident, aged 61. Graduate of Northwestern University Medical School, Chicago, 1947. Licensed in California in 1949. Dr. Hough was a member of the Inyo-Mono County Medical Society.

Keasbey, Louisa, Los Angeles. Died December 22, 1979 in Long Beach, aged 82. Graduate of Cornell University Medical College, New York, 1924. Licensed in California in 1949. Dr. Keasbey was a member of the Los Angeles County Medical Association.

Larson, Carl F., Sausalito. Died November 29, 1979, aged 93. Graduate of the University of Oregon Medical School, Portland, 1914. Licensed in California in 1914. Dr. Larson was a retired member of the Marin Medical Society.

Norman, Guido Frederick, San Francisco. Died December 2, 1979 in San Francisco of myocardial infarct, aged 83. Graduate of the University of California Medical School, Berkeley-San Francisco, 1923. Licensed in California in 1923. Dr. Norman was a member of the San Francisco Medical Society.

Novack, Benjamin F., Hayward. Died February 5, 1979 of arteriosclerotic cardiovascular disease, aged 66. Graduate of the University of Illinois College of Medicine, Chicago, 1940. Licensed in California in 1946. Dr. Novack was a member of the Alameda-Contra Costa Medical Association.

Paoli, Theodore H., Daly City. Died December 25, 1979 in San Francisco, aged 69. Graduate of the Creighton University School of Medicine, Omaha, 1934. Licensed in California in 1934. Dr. Paoli was a retired member of the San Francisco Medical Society.

Pickering, Paul P., San Diego. Died December 27, 1979, aged 67. Graduate of Rush Medical College, Chicago, 1941. Licensed in California in 1945. Dr. Pickering was a member of the San Diego County Medical Society.

QUITT, LOUIS I., Van Nuys. Died July 7, 1979 of myocardial infarct, aged 58. Graduate of the University of Toronto Faculty of Medicine, 1952. Licensed in California in 1953. Dr. Quitt was a retired member of the Los Angeles County Medical Association.

RICHARD, DONAT R., Glendale. Died October 17, 1979, aged 69. Graduate of McGill University Faculty of Medicine, Montreal, 1937. Licensed in California in 1947. Dr. Richard was a member of the Los Angeles County Medical Association.

RODA, DAVID DELA CRUZ, Antioch. Died December 5, 1979 in Oakley of heart disease, aged 56. Graduate of Manila Central University College of Medicine, Manila, 1952. Licensed in California in 1957. Dr. Roda was a member of the Alameda-Contra Costa Medical Association.

SCHALLIG, DOROTHY WALSH, Sacramento. Died November 17, 1979 in Sacramento, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1928. Licensed in California in 1928. Dr. Schallig was a retired member of the Sacramento County Medical Society.

STEWART, FLETCHER C., Seal Beach. Died August 6, 1979, aged 79. Graduate of the University of Nebraska College of Medicine, Omaha, 1924. Licensed in California in 1953. Dr. Stewart was a retired member of the Orange County Medical Association.

WELTY, GORDON A., San Jose. Died December 19, 1979 in San Jose, aged 34. Graduate of the University of California, Los Angeles, School of Medicine, 1972. Licensed in California in 1973. Dr. Welty was a member of the Santa Clara County Medical Society.

WILLIAMS, LUINS H., San Francisco. Died December 18, 1979 in San Francisco, aged 66. Graduate of Meharry Medical College, Nashville, 1938. Licensed in California in 1942. Dr. Williams was a member of the San Francisco Medical Society.

Washington State Medical Association

BAKER, WILLIAM Y., Seattle. Died October 31, 1979, aged 70. Graduate of the University of Nebraska College of Medicine, Omaha, 1933. Licensed in Washington in 1935. Dr. Baker was a member of the King County Medical Society.

BELL, WILLIAM M., Seattle. Died August 10, 1979, aged 55. Graduate of Washington College of Physicians and Surgeons, Seattle, 1964. Dr. Bell was a member of the King County Medical Society and Washington State Medical Association.

BUCKLEY, HAROLD D., Yakima. Died May 10, 1979, aged 51. Graduate of the University of Washington School of Medicine, Seattle, 1953. Licensed in Washington in 1954. Dr. Buckley was a member of the Yakima Medical Society.

CORBETT, DONALD G., Spokane. Died October 27, 1979, aged 80. Graduate of Pennsylvania State University College of Medicine, Hershey, 1934. Licensed in Washington in 1948. Dr. Corbett was a member of the Spokane County Medical Society.

DEMING, J. EDMUND, Tacoma. Died October 24, 1979, aged 60. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1944. Licensed in Washington in 1946. Dr. Deming was a member of the Pierce County Medical Society.

FRITZ, KIRKLAND JOHN, Richland. Died January 10, 1980, aged 43. Graduate of the University of Washington School of Medicine, Seattle, 1963. Licensed in Washington in 1971. Dr. Fritz was a member of the Benton-Franklin Medical Society.

JOHNSTON, JOHN DALLAS HOWARD, Everett. Died May 28, 1979, aged 48. Graduate of the University of British Columbia Faculty of Medicine, Vancouver, 1958. Licensed in Washington in 1963. Dr. Johnston was a member of the Snohomish County Medical Society.

KEPL, MAXWELL, F., Spokane. Died March 10, 1979, aged 65. Graduate of Northwestern University Medical School, Chicago, 1940. Licensed in Washington in 1946. Dr. Kepl was a member of the Spokane Medical Society.

LYDA, WOOD, Seattle. Died January 8, 1980, aged 61. Graduate of Washington University School of Medicine, St. Louis, 1943. Licensed in Washington in 1947. Dr. Lyda was a member of King County Medical Society.

SLEDGE, JAMES NATHAN, Spokane. Died October 15, 1979, aged 62. Graduate of Washington University School of Medicine, St. Louis, 1943. Licensed in Washington in 1949. Dr. Sledge was a member of Spokane County Medical Society.

WILLIAMS, ROBERT H., Seattle. Died November 5, 1979, aged 70. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1934. Licensed in Washington in 1948. Dr. Williams was a member of the King County Medical Society.

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(Continued on Page 20)

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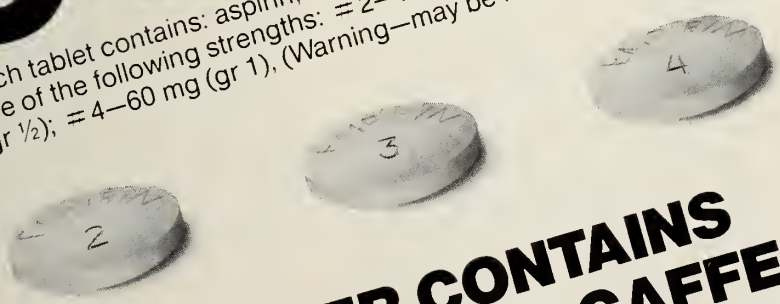

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29 YEAR OLD BOARD ELIGIBLE INTERNIST will finish training and seeks practice opportunity in July 1980 in Northern California, Oregon, or Washington state. Steven Walker, 2153 So. Columbine, Denver, CO 80210.

FAMILY DOCTOR: Practice sought in central or eastern San Diego County. Partnership size or potential. Terms desired for immediate or future takeover. (714) 464-6911 evenings, or Box 6105, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIAN with 10 years experience in preventive and occupational medicine and postgraduate training for 4 years, seeks position in San Francisco/Bay Area in medical outpatient clinic. Write Box 6020, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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BUYING or SELLING any type Medical Practice contact California Professional Practices, 2555 Huntington Drive, Suite D, San Marino, CA 91108. (213) 796-9262, Eve (213) 355-3983.

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(Continued on Page 24)

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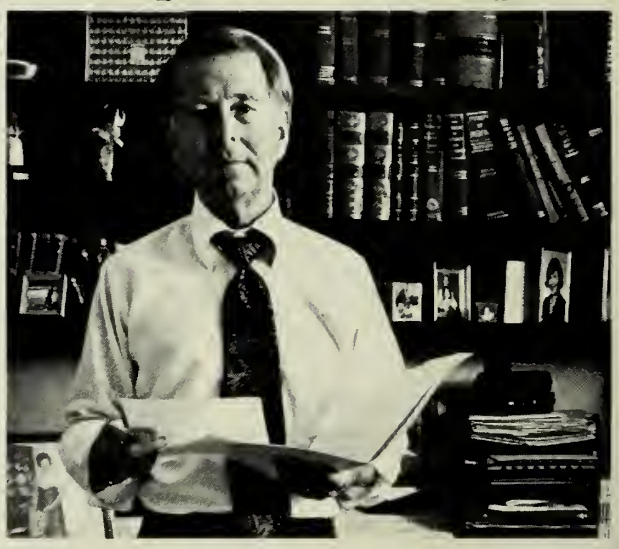

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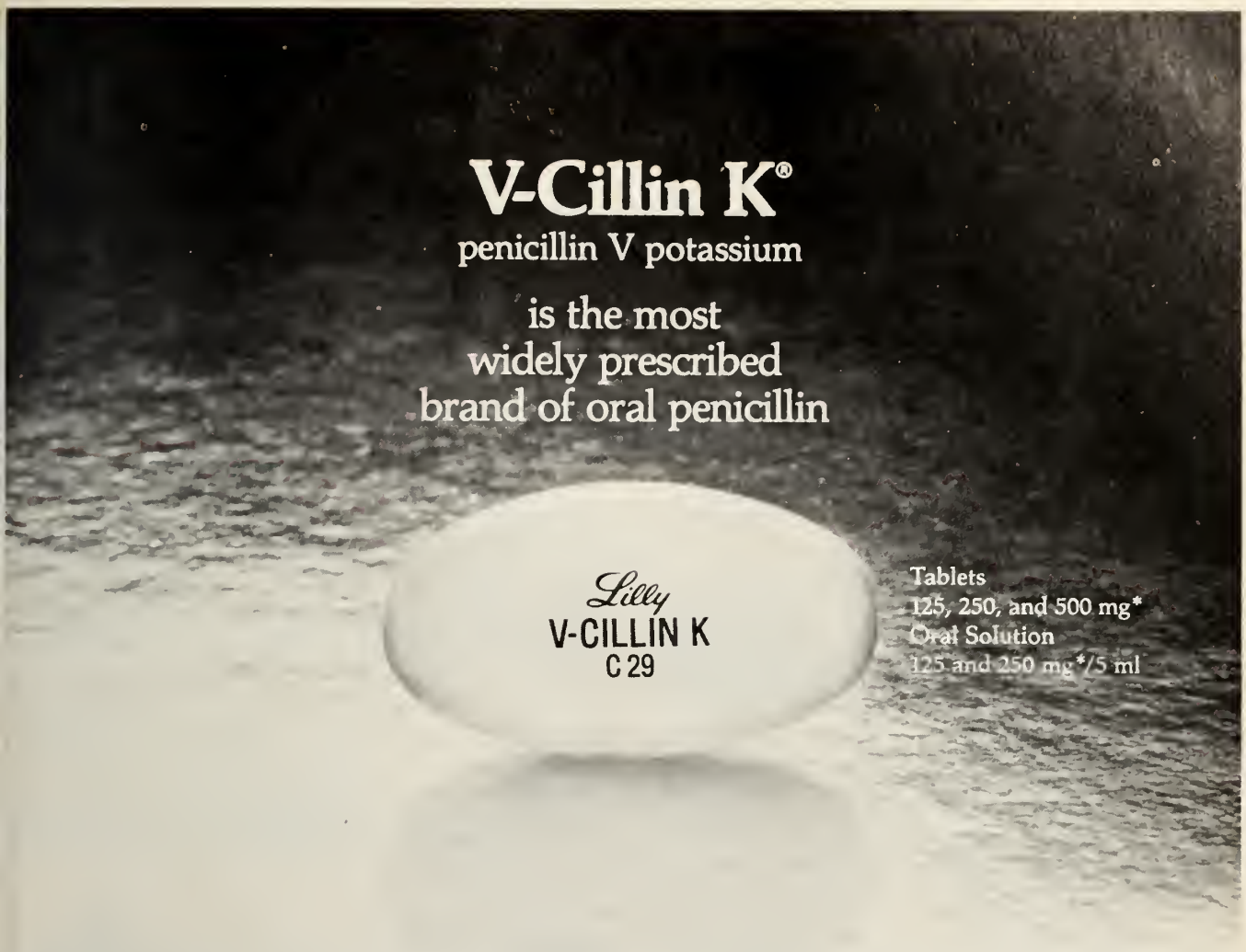

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(Continued from Page 21)

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FULLY EQUIPPED INTERNAL MEDICINE OFFICE, or related field, to share expenses. Mill Valley, California. Box 6104, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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PHYSICIAN SHORTAGE Redding Medical Suites. Downtown location convenient to both hospitals. Reasonable rents. Serge (916) 244-0600, Res (916) 241-4099 or Mary (415) 376-0762.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

HORMONAL FUNCTION AND THE KIDNEY—Volume 4 of CONTEMPORARY ISSUES IN NEPHROLOGY—Series Editors: Barry M. Brenner, MD, Samuel A. Levine, Professor of Medicine, Harvard Medical School; Director, Renal Division and Laboratory of Kidney and Electrolyte Physiology, Peter Bent Brigham Hospital, Boston; and Jay H. Stein, MD, Professor and Chairman, Department of Medicine and Director, Division of Renal Diseases, the University of Texas Health Science Center at San Antonio. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1979. 296 pages, $29.00.

HOW TO SURVIVE MODERN TECHNOLOGY—A Crash Course in Protecting Your Health From Hidden Hazards of Modern Living—Charles T. McGee, MD. Ecology Press, P.O. Box 694, Alamo, CA (94507), 1979. 281 pages, $5.95 (paperback).

THE LOW-CHOLESTEROL FOOD PROCESSOR COOKBOOK—Suzanne S. Jones; Foreword by Kevin E. Conboy, MD. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1980. 210 pages, $9.95.

RADIOPHARMACEUTICALS II: Proceedings of the Second International Symposium on Radiopharmaceuticals, March 19-22, 1979, Seattle. Society of Nuclear Medicine, 475 Park Avenue South, New York City (10016), 1979. 809 pages, $40.00 (soft cover).

RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF PITUITARY TUMORS—Edited by John A. Linfoot, MD, Physician-In-Chief, Donner Pavilion, Lawrence Berkeley Laboratory, University of California, Berkeley. Raven Press, 1140 Avenue of the Americas, New York City (10036), 1979. 442 pages, $38.00.

SNEEZING, WHEEZING AND SCRATCHING—Doris J. Rapp, MD. The ECR Collection, P.O. Box 615, Los Altos, CA (94022), 1974. 24 pages, $1.50 (paperback); quantity discounts.

SPECIAL TOPICS IN ENDOCRINOLOGY AND METABOLISM—Volume 1—Editors: Margo P. Cohen, Wayne State University School of Medicine, Detroit; and Piero P. Foà, Wayne State University School of Medicine. Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1979. 144 pages, $18.00.

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WEDNESDAY, APRIL 16, 1980 • 1:30 to 5:30 P.M.

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- RICHARD K. MYLER, MD
  Co-Director Cardiac Catheterization Laboratory, St. Mary's Hospital, San Francisco, Associate Clinical Professor Medicine, University California, San Francisco
- JOHN B. SIMPSON, MD
  Clinical Assistant Professor Medicine (Cardiology), Stanford University School of Medicine, Stanford, CA
- CHARLES J. TEGTMEYER, MD
  Professor Radiology, Associate Professor Anatomy, Director Angiography, University of Virginia School of Medicine, Charlottesville, VA
- LEWIS WEXLER, MD
  Associate Professor Diagnostic Radiology, Stanford University School of Medicine, Stanford, CA

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- EUGENE J. ELLIS, MD
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This listing of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

March 30-April 5—**Obstetric Anesthesia.** Ohio State University, Dept. of Anesthesiology, at Sheraton Waikiki Hotel, Oahu, Hawaii. One week. Contact: John S. McDonald, MD, Dept. of Anesthesiology, OSU, 410 W. 10th Ave., Columbus, OH 43210. (614) 422-5591.

CANCER

March 15-16—**Pharmaceutical Aspects of Cancer Care—15th Annual San Francisco Cancer Symposium.** West Coast Cancer Foundation and American Cancer Soc. at Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: West Coast Cancer Foundation, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

April 12—**New Developments in Oncology.** San Francisco Regional Cancer Foundation and American Cancer Society at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. $15. Contact: Terry Sheehy, PhD, S.F. Regional Cancer Fndn., 14th and Lake, San Francisco 94118. (415) 221-2132.

EMERGENCY MEDICINE

March 17-21—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

March 20—**Radiology in the Emergency Department.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

April 12-13—**Symposium on Survival: An Analysis of Disaster Planning.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

April 12-19—**Emergency Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

April 17—**Infectious Disease for Emergency Physicians.** Goleta Valley Community Hospital and Assn. for Emergency Physicians for Ventura and Santa Barbara Counties at Goleta Valley Hosp., Santa Barbara. Thursday. 1½ hrs. CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

April 17—**Neurologic Emergencies.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

April 21-25—**Postgraduate Institute for Emergency Physicians,** Symposium I. UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

April 24-25—**Emergency Medicine Trauma Seminar—2nd Annual.** DREW. Thursday-Friday.

April 25-27—**Advanced Cardiac Life Support Provider, Recertification and Instructor Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, Education Dept., 2310 Mason St., San Francisco 94133. (415) 956-5900.

May 5-11—**Emergency Surgical Problems.** White Memorial Medical Center and LLU at Honolulu and Maui, Hawaii. One week. 24 hrs. $250. Contact: Dir., Cont. Med. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000, ext. 1460.

May 11-17—**Modern Trends in Emergency Medicine.** Univ. of Hawaii, John A. Burns School of Medicine, Hawaii. One week. Contact: Delia M. Chang, CME, Univ. of Hawaii, John A. Burns Sch. of Medicine, 1960 East-West Rd., Honolulu 96822.

May 14—**Emergency Medicine Symposium.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

May 15—**ENT Emergencies.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

May 19-23—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 40 hrs. $300.

May 27-31—**American College of Emergency Physicians, Cali-**

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

fornia Chapter—1980 Scientific Assembly. ACEP, Calif. Chap., and UCSD at Hotel del Coronado, Coronado. Tuesday-Saturday. Contact: UCSD.

June 10-13—**Radiology in the Emergency Room Department.** UCSF at Fairmont Hotel. Tuesday-Friday.

June 17—**Death in the Emergency Department.** St. John's Hospital and Assn. for Emergency Physicians for Ventura and Santa Barbara Counties at St. John's Hospital, Oxnard. Tuesday; 8:00 p.m. 1½ hrs CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

June 19—**Plastic Surgery in the Emergency Department.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

June 23-27—**Advanced Emergency Medicine.** STAN. Monday-Friday. 25 hrs. $290.

June 23-27—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

June 27-28—**Ophthalmology and ENT for Emergency Room Physicians.** PMC. Friday-Saturday. 12 hrs.

July 14-18—**Medical Management of EMS Systems.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs.

July 21-25—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

July 25-27—**Advanced Cardiac Life Support Provider, Recertification and Instructor Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, Education Dept., 2310 Mason St., San Francisco 94133. (415) 956-5900.

August 11-15—**Postgraduate Institute for Emergency Physicians, Symposium I:** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

MEDICINE

March 16-19—**Basic Cardiology for the Primary Care Physician.** UCSF at Yosemite. Sunday-Wednesday.

March 21-23—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Jack Tar Hotel, San Francisco. Friday-Sunday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

March 24-26—**4th Annual Review and Update of the Immunology and Clinical Practice of Allergy.** USCD at Hilton, San Diego. Monday-Wednesday. 20 hrs. $225.

March 24-April 4—**Intensive Review of Internal Medicine.** USC. Two weeks.

March 26-28—**Endocrine Glands in Health and Disease.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday.

March 27-29—**Scientific Basis of Respiratory Care: Present State-of-the-Art and Future Directions.** American College of Chest Physicians at Sheraton-Palace, San Francisco. Thursday-Saturday. 16 hrs. $165, ACCP members; $185, nonmembers. Contact: Dale E. Braddy, Dir. of Ed., ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200.

March 29-April 5—**Infectious Diseases.** Univ. of Washington School of Medicine at Naniloa and Kona Surf Hotels, Hilo, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 7-16—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 9—**Cardiovascular Disease.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Memorial Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

April 9—**Asthma in Childhood.** See Pediatrics, April 9.

April 9-12—**Coronary Artery Disease: A Comprehensive Review.** American Medical Association and American College of Cardiology at Century Plaza, Los Angeles. Wednesday-Saturday. 32 hrs. Contact: AMA, Dept. of Meeting Services, 535 N. Dearborn, Chicago 60610. (312) 751-6000.

April 9-June 11—**Practical Dermatology for the Practicing Internist.** UCLA. 10 Wednesday evenings. 20 hrs.

April 10-11—**Advances in Infectious Diseases: Prophylactic Antibiotics in Medicine and Surgery.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday. 14 hrs. $150.

April 11—**Bronchial Asthma.** UCD at Hyatt on Union Square, San Francisco. Friday.

April 12-19—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

April 16—**Percutaneous Angioplasty.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 4 hrs. $35. Contact: Janie Sternal, Coordinator, Cont. Med. Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8904 or (213) 488-8123.

April 18-20—**Rheumatology: The New Decade.** UCSF, The Cypress Foundation and Monterey Co. Medical Society at Del Monte Hyatt House, Monterey. Friday-Sunday. 16 hrs. $155. Contact: UCSF.

April 25-27—**New Concepts in Clinical Electrocardiography.** American College of Cardiology at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 26-27—**Practical Rheumatology.** UCLA. Saturday-Sunday.

April 28-30—**Pediatric Dermatology.** STAN at Rancho Mirage. Monday-Wednesday. 18 hrs. $195.

April 30—**Office Management of Hypertension.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Wednesday. 4 hrs.

May 2-4—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Sunday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

May 2-4—**Headache Management: Therapeutic Workshops.** UCLA at Newporter Inn, Newport Beach. Friday-Sunday.

May 3—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

May 9-11—**The Many Faces of Headache.** UCD at Holiday Inn, Napa Valley. Friday-Sunday.

May 10—**Cardiology Conference.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

May 15-17—**Acute Myocardial Infarction.** PMC at St. Francis Hotel, San Francisco. Thursday-Saturday. 15 hrs.

May 16-18—**Cardiac Rehabilitation.** International Medical Education Corp. at Jack Tar Hotel, San Francisco. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

May 19-24—**4th Bi-Annual Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday.

May 30—**Team Approach to Arthritis.** PMC and Arthritis Foundation. Friday. 6 hrs. $85.

May 31-June 1—**Pediatric Dermatology.** UCLA. Saturday-Sunday.

May 31-June 1—**Kidney Disease—20th Annual Scientific Symposium.** Kidney Foundation of Southern Calif. at Bonaventure Hotel, Los Angeles. Saturday-Sunday. Contact: Micki Faris, Kidney Fndn. of So. Calif., 6820 La Tijera Blvd., Suite 111, Los Angeles 90045. (213) 641-8152.

June 2-6—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday. 34 hrs.

June 9-13—**Advances in Internal Medicine.** UCSF. Monday-Friday. 34 hrs.

June 11-14—**7th Annual Symposium on Clinical Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Wednesday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 18—**The Diagnosis and Management of the Newborn With Cardiorespiratory Disease.** American Heart Assn., Greater Los Angeles Affiliate, at New Otani Hotel, Los Angeles. Wednesday. 6 hrs. $50, member; $60, nonmember. Contact: Mary Frances Flynn, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

June 20-21—**Medical Knowledge Self Assessment—Group C.** American College of Physicians and PMC at Hyatt Regency, San Francisco. Friday-Saturday. Contact: PMC.

June 27-29—**Hepatobiliary Disease in Clinical Practice.** American College of Physicians at Holiday Inn on Union Square, San Francisco. Friday-Sunday. 15 hrs. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

July 8-10—**Podiatric Dermatology.** STAN. Tuesday-Thursday. 17 hrs.

July 12-19—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 23 hrs. $290.

August 2—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

August 8-10—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

August 15-17—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

OBSTETRICS AND GYNECOLOGY

March 22-23—**Contraception: Current Research and Multidisciplinary Applications.** See Of Interest To All, March 22-23.

May 12-14—**Recent Advances in Ob/Gyn.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

May 16-18—**Ob/Gyn.** UCLA at Ojai Valley Inn, Ojai. Friday-Sunday. 12 hrs. $300.

June 5-7—**Gynecologic Urology: Theory and Practice, Basic and Advanced.** Mem. Hosp. Med. Ctr.-UCI Ctr. for Health Education at Inn at the Park, Anaheim. Thursday-Saturday. 20 hrs. $300. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 10-16—**Obstetrics/Gynecology.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

PEDIATRICS

April 4-5—**Pediatric Topics 1980.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 9 hrs. $80.

April 9—**Asthma in Childhood.** LLU. Wednesday. 4 hrs. $30.

April 11-12—**Pediatric Symposium—22nd Annual.** So. Calif. Permanente Medical Group at Sheraton Hotel, Anaheim. Friday-Saturday. Contact: Shirley Gach, Ed. and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

April 26-27—**The Special Child.** See Psychiatry, April 26-27.

April 28-30—**Pediatric Dermatology.** See Medicine, April 28-30.

May 3—**Pediatric Dermatology Seminar.** See Medicine, May 3.

May 5-9—**Pediatric Review—10th Annual.** USC. Monday-Friday.

May 7-9—**Care of the Sick Newborn.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 18 hrs. $130. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 8-10—**Annual Pediatrics Course.** UCSF. Thursday-Saturday.

May 21-25—**Pediatrics for the Primary Care Physician.** UCD at Red Lion Motor Inn, Sacramento. Wednesday-Sunday. 18 hrs.

May 31-June 1—**Pediatric Dermatology.** See Medicine, May 31-June 1.

June 14-21—**Pediatric Workshop.** USC at Royal Lahaina, Maui, Hawaii. One week. 22 hrs. $325.

June 18—**The Diagnosis and Management of the Newborn With Cardiorespiratory Disease.** See Medicine, June 18.

August 2—**Pediatric Dermatology.** See Medicine, August 2.

PSYCHIATRY

March 15—**The Void—Treatment of a Narcissistic Patient.** No. Calif. Psychiatric Society and McAuley Institute at St. Mary's Hospital, San Francisco. Saturday. 3 hrs. $15. Contact: George L. Ponomareff, MD, 2457 Grove Way, Suite 102, Hayward 94546.

March 21-23—**Narcissism—A Multidimensional View.** UCSF. Friday-Sunday.

April 7-May 22—**MRI Workshop Series.** Mental Research Institute, Palo Alto. Series of 1-4 day workshops on a variety of topics related to mental health. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

April 10-May 15—**Films and Psychiatry.** PMC. Thursday evenings. 18 hrs. $75.

April 26-27—**The Special Child.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

May 5-9—**American Psychiatric Association.** Hilton, San Francisco. Monday-Friday. Contact: APA, 1700 18th St. NW, Washington, DC 20009.

June 22-27—**Comparative Psychotherapies.** USC at Hilton, San Diego. Monday-Friday.

RADIOLOGY AND PATHOLOGY

March 24-28—**Abdominal Radiology Update 1980.** UCSD at Vacation Village, San Diego. Monday-Friday. 36 hrs.

April 10—**Bone and Joint Clinical-Pathological-Radiological Correlation Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 13-18—**American Association of Pathologists.** Anaheim. Sunday-Friday. Contact: AAP, 9650 Rockville Pike, Bethesda, MD 20014.

May 10—**Chest Radiology: Update 1980.** Northern Calif. Radiological Society at Red Lion Inn, Sacramento. Saturday. 7¼ hrs. $75. Contact: Richard C. Gross, MD, Roseville Community Hosp., Roseville 95678. (916) 783-9111, ext. 543.

May 17—**Recent Advances in Pathology.** UCSF at Hyatt on Union Square, San Francisco. Saturday. 8 hrs. $90.

May 28-30—**Present Concepts in Diagnostic Radiology.** Letterman Army Medical Center, San Francisco. Wednesday-Friday. 18 hrs. Contact: R. S. Pakusch, MD, or D. Kumar, MD, Dept. of Radiology, Letterman Army Med. Ctr., San Francisco 94129. (415) 561-3761.

June 6-8—**Spring Diagnostic Ultrasound Conference—5th Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 17 hrs. $250. Contact: Nathan Green, MD, 15107 Vanowen St., Van Nuys 91405.

June 10-13—**Radiology in the Emergency Room Department.** See Emergency Medicine, June 10-13.

June 16-25—**Radiology of Bone and Joint Disease.** UCSD at Hotel del Coronado, Coronado (June 16-19) and Kauai Surf Resort Hotel, Kauai, Hawaii (June 23-25). 7 days. 29 hrs. $500 (or $300 for first part; $200, second part).

June 22-27—**Pathology of the Lung.** UCSD. One week. 50 hrs. $450.

August 9-16—**Radiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

March 15-19—**Controversial Areas in Surgery—17th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 19-23—**Vascular Surgery—8th Annual Symposium.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 25-29—**3rd U.S. Intraocular Lens Symposium and 7th Scientific Session.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Tuesday-Saturday. 30 hrs. Contact: Debbi Miller, Dir. of Mtg. Services, AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 395-3937.

April 3-4—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 10-11—**Advances in Infectious Diseases: Prophylactic Applications in Medicine and Surgery.** See Medicine, April 10-11.

April 18-19—**Workshop on Orthopedic Injuries.** PMC. Friday-Saturday.

April 19-20—**Office Orthopedics/Office Urology.** UCLA. Saturday-Sunday.

April 24-25—**11th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. Contact: Mrs. Lu Hendricks, JSEI, UCLA Sch. of Med., Los Angeles 90024.

April 24-26—**General Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday.

April 26-May 3—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

April 28-30—**American Association for Thoracic Surgery.** Hilton Hotel, San Francisco. Monday-Wednesday. Contact: AATS, 6 Beacon St., Suite 620, Boston, MA 02108.

May 4-5—**Controversies in Surgery of the Colon, Rectum and Anus—5th Annual Clarence E. Stafford Memorial Surgical Symposium.** White Memorial Medical Center and LLU at Century Plaza Hotel, Los Angeles. Sunday-Monday. 11 hrs. Contact: Dir., Cont. Med. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000.

May 5-6—**Neurosurgical Contributions to Daily Medical Practice.** UCSD at Vacation Village, San Diego. Monday-Tuesday. 16 hrs. $160.

May 5-11—**Emergency Surgical Problems.** See Emergency Medicine, May 5-11.

May 9-10—**Combined Otolaryngologic/Orthognathic Symposium.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Friday-Saturday. 12 hrs. $195.

May 10—**Photocoagulation Therapy Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

May 15-17—**Nasal Plastic and Reconstructive Surgery.** PMC at Clift Hotel, San Francisco. Thursday-Saturday. 15 hrs. $250.

May 18-22—**American Urological Association.** Hilton, San Francisco. Sunday-Thursday. Contact: AUA, 1120 N. Charles St., Baltimore, MD 21201.

May 29-31—**Oto '80.** Project HEAR at St. Francis Hotel, San Francisco. Thursday-Saturday. 24 hrs. $485. Contact: Judy Staton Thielke, Project HEAR, 1801 Page Mill Rd., Palo Alto 94304. (415) 494-2000.

June 3-6—**25th Annual Samuel Higby Camp Lectureship and 15th Annual Scientific Program of the LeRoy C. Abbott Orthopaedic Society.** UCSF. Tuesday-Friday. 14 hrs. Contact: Mark Parsons, Alumni Sec., UCSF, Room U471, San Francisco 94143. (415) 666-1166.

June 5-6—**Neurosurgery Postgraduate Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Friday. 17 hrs. $225.

June 6-7—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

June 7—**Glaucoma Surgery Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks,

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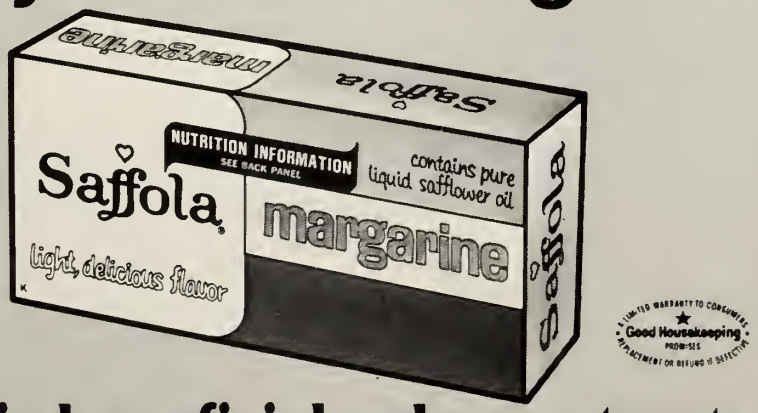

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JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

June 7-13—**Orthopedic Review Course.** UCSF at Hyatt on Union Square, San Francisco. One week. 50 hrs.

June 8-14—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

June 11—**Problems in Postoperative Management and the Surgical Intensive Care Unit.** LLU. Wednesday. 4 hrs. $30.

June 14-21—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $325.

June 19-20—**Office Orthopedics.** USC. Thursday-Friday.

June 19-21—**Highlights of Ophthalmology.** PMC at Hyatt Regency, San Francisco. Thursday-Saturday. $225.

July 12-19—**Cardiovascular Medicine and Surgery: An Advanced Course.** See Medicine, July 12-19.

OF INTEREST TO ALL PHYSICIANS

March 15—**Medical Treatment of Alcoholism.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7 hrs.

March 15-16—**Practical ENT for Primary Care Physicians.** UCLA. Saturday-Sunday.

March 18-21—**Clinical Management.** STAN at The Lodge, Pebble Beach. Tuesday-Friday. 12 hrs. $150.

March 18-22—**Sports Medicine.** University of Hawaii School of Medicine at Princess Kaiulani Hotel, Waikiki, Honolulu, Hawaii. Tuesday-Saturday. 18 hrs. $200. Contact: Hawaii Conference Services, P.O. Box 25055, Honolulu 96825. (808) 377-6445.

March 19-21—**American Society for Clinical Pharmacology and Therapeutics.** Fairmont Hotel, San Francisco. Wednesday-Friday. Contact: E. H. Funk, Jr., MD, ASCPT, 1718 Gallagher Rd., Norristown, PA 19401.

March 22—**Otolaryngology for the Primary Care Physician.** Institute for Medical Education and Research, San Diego. Saturday. Contact: Inst. for Med. Ed. and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126.

March 22-23—**Contraception: Current Research and Multidisciplinary Applications.** UCSF. Saturday-Sunday. Contact: UCSF, Cont. Ed. Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

March 24-28—**Postgraduate Institute for Primary Care Physicians.** UCSD at Vacation Village, San Diego. Monday-Friday.

March 31-April 2—**Football Injury Workshop.** Center for Sports Medicine, St. Francis Memorial Hospital at Jack Tar Hotel, San Francisco. Monday-Wednesday. $165. Contact: Ctr. for Sports Medicine, St. Francis Mem. Hosp., 900 Hyde St., San Francisco 94109. (415) 775-4321, ext. 3370.

April 6-9—**Clinical Dermatology for the Family Practitioner.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Wednesday. 14½ hrs. $125.

April 8, 15, 22, 29, May 3—**Therapeutic Movement, Manipulation and Massage.** UCLA. Tuesdays.

April 9-12—**Nosocomial Infection.** Memorial Hospital Medical Center-UCI Center for Health Education. Wednesday-Saturday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 12—**Medical Applications of Exercise for the Primary Care Physician.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 9 hrs.

April 13-17—**Association for the Advancement of Medical Instrumentation—15th Annual Meeting.** Hyatt Regency, San Francisco. Sunday-Thursday. Contact: AAMI, 1901 N. Ft. Myer Dr., Suite 602, Arlington, VA 22209. (703) 525-4890.

April 17-19—**Wound Management Workshop.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

April 21-25—**1980 Family Practice Review.** PMC at Hilton Hotel, Oakland Airport. Monday-Friday. 27 hrs. $350.

April 24-27—**Postgraduate Institute.** CMA and USC at Ahwahnee Hotel, Yosemite. Thursday-Sunday. Contact: Charlotte Newhart, CMA.

May 1-2—**Therapeutic Drug Monitoring.** PMC. Thursday-Friday. 12 hrs.

May 1-4—**4th Annual Basic Clinic Hypnosis Workshop.** UCI at Balboa Bay Club, Newport Beach. Thursday-Sunday. 30 hrs. $310.

May 2-3—**Providence Hospital Annual Spring Seminar.** Claremont Hotel, Oakland. Friday-Saturday. Contact: Medical Staff Office, Providence Hosp., 3100 Summit St., Oakland 94623. (415) 835-4500, ext. 2032.

May 3-4—**Holistic Medicine: The Pursuit of Wellness.** UCSF and State Dept. of Health Services at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: UCSF Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

May 10, 24—**Clinical Nutrition.** UCLA. Two Saturdays.

May 12-15—**Aerospace Medical Association.** Disneyland Hotel, Anaheim. Monday-Thursday. Contact: R. R. Hessberg, MD, Washington Nat'l Airport, Washington, DC 20001.

May 13-19—**Basic Diving Medicine.** UCSF at Fresno. One week.

May 14—**Deafness and Its Management.** LLU. Wednesday. 4 hrs. $30.

May 16-18—**2nd Annual National Symposium on Sexuality and Disability.** UCSF at Claremont Hotel, Berkeley. Friday-Sunday. Contact: UCSF Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

May 17-18—**Advanced Therapeutics in Clinical Nutrition.** St. Francis Memorial Hospital and American Society of Parenteral and Enteral Nutrition at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: Elena Tinloy, PharmD, St. Francis Mem. Hosp., P.O. Box 7726, San Francisco 94120. (415) 775-4321, ext. 3323.

May 18-23—**Fingers-to-the-Toes: An Orthopaedic Approach for the Family Practitioner.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Friday.

May 19-23—**7th Annual Family Practice Refresher Course.** UCLA and Santa Monica Hospital Medical Center at Sheraton-Miramar, Santa Monica. Monday-Friday. Contact: UCLA.

June 7-8—**Nutrition: Myths and Realities.** UCSF and Institute for the Study of Human Knowledge at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

June 11-13—**Clinical Application of Hyperbaric Oxygen—5th Annual Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 24 hrs. Contact: G. B. Hart, MD, Dir., Baromedical Dept., Mem. Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801.

June 13-15—**American Medical Association Regional Meeting.** Hyatt on Union Square, San Francisco. Friday-Sunday. Contact: AMA, Dept. of Meeting Services, 535 N. Dearborn St., Chicago 60610. (312) 751-6503.

June 16-21—**Family Practice Refresher Course—11th Annual.** UCI at Marriott Inn, Newport Beach. Saturday-Thursday. 49 hrs. $335.

August 10-14—**Western Hemisphere Nutrition Congress VI.** American Medical Association, American Institute of Nutrition, Nutrition Society of Canada, at Biltmore Hotel, Los Angeles. Sunday-Thursday. Contact: AMA, Dept. of Foods and Nutrition, 535 N. Dearborn St., Chicago 60610.

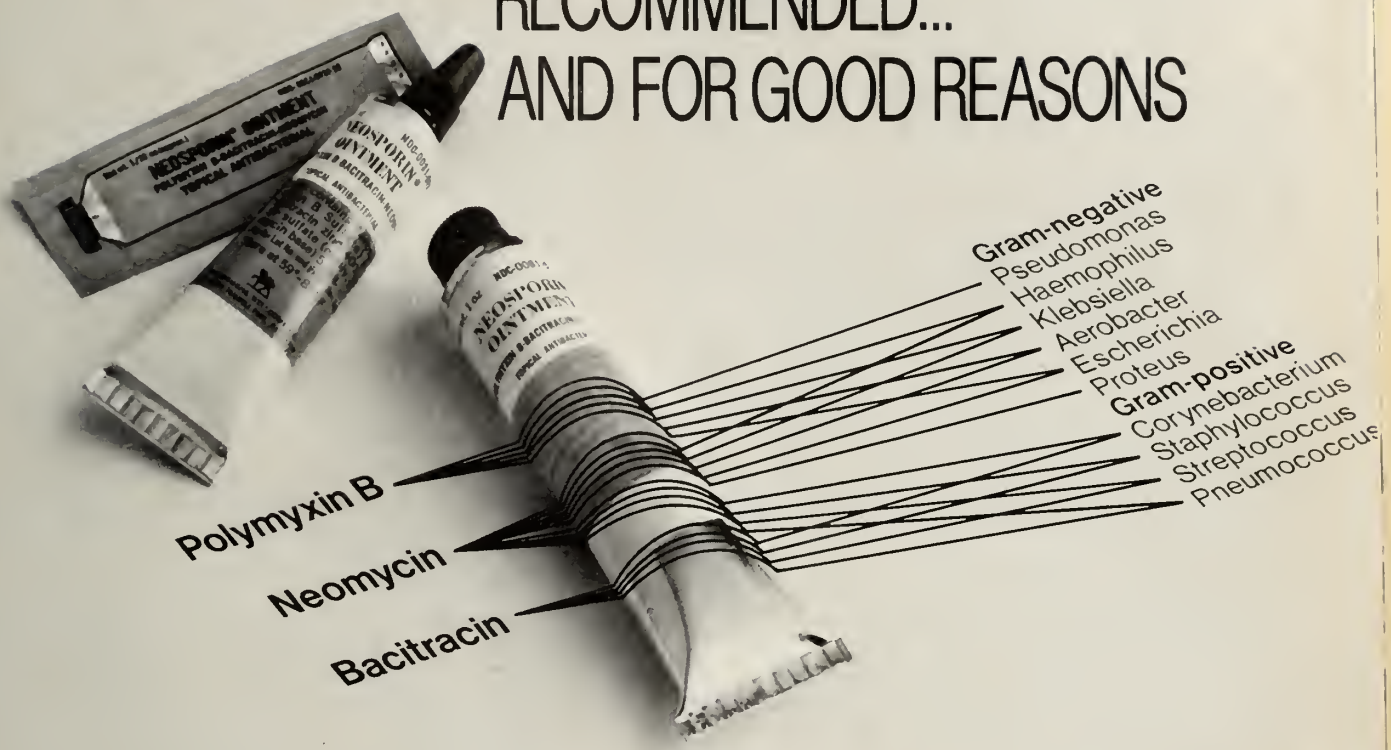
August 14-17—**Sexuality.** Orange County and American Urological Associations at Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

August 24-29—**Family Practice Refresher Course—8th Annual.** UCD at Del Monte Hyatt, Monterey. Sunday-Friday.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

(Continued on Page 32)

IT'S HIGHLY RECOMMENDED... AND FOR GOOD REASONS



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WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

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ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

March 20—**Treatment Outcome Study, Harborview Community Health Center—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

March 26—**Utilization of Midlevel Practitioners—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

May 1—**Child and Community Psychiatry—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

May 28—**Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday, 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

June 19—**Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

MONTANA

March 26-28—**The Eye and Internal Disease—Univ. of Wash. Internal Medicine Review Sessions.**

March 26, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 27, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

March 28, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 9—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 16-18—**Office Gynecology—Univ. of Wash. Internal Medicine Review Sessions.**

April 16, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 17, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

April 18, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 18-19—**Montana Medical Association's 1980 Interim Meeting.** Helena. Friday-Saturday. Contact: G. Brian Zins, Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

May 7—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28-30—**Nuclear Medicine for Internists—Univ. of Wash. Internal Medicine Review Sessions.**

May 28, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 29, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

May 30, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 52 West Pine, Missoula, MT 59801. (406) 549-3782.

June 11-13—**Transient Ischemic Attack and Stroke; Seizure Disorders—Univ. of Wash. Internal Medicine Review Sessions.**

June 11, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

June 12, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

June 13, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

IDAHO

March 15-22—**Sports Medicine.** Sun Valley. Saturday-Saturday. Sun Valley Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 17—**Shock in Pregnancy—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

March 25—**Pediatric Arthritis and Immunology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

April 14—**Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

April 22—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

May 19—**Hypertension and Pregnancy—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 20—**Dysmorphology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony's Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

MEDICINE

April 25—**Endocrinology for the Clinician.** Portland. Friday. Jantzen Beach Red Lion Motor Inn. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OTOLARYNGOLOGY

March 28-29—**Oregon Academy of Otolaryngology 39th Annual Postgraduate Convention.** Portland. Friday-Saturday. Jantzen Beach Red Lion Motor Inn. Contact: Miss Rebecca Tarshis, Executive Secretary, P.O. Box 13155, Portland, OR 97213.

OF INTEREST TO ALL PHYSICIANS

April 11—**Preventive Health Care for Women.** Portland. Friday. Jantzen Beach Red Lion Motor Inn. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 17-20—**American College of Physicians Review Course.** Portland, Tuesday-Friday. Jantzen Beach Thunderbird. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 25-27—**Symposium on Sports Medicine.** Eugene, Wednesday-Friday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

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WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

March 15-22—**Sports Medicine.** Sun Valley, Idaho. Saturday-Saturday. Sun Valley Inn. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 17-28—**Rehabilitation Medicine Review.** Seattle. Two weeks. University Towers Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 18—**Shock in Pregnancy—Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

March 21-22—**Days of Pediatrics.** Tacoma. Friday-Saturday. Mary Bridge Children's Hospital. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98450. (206) 627-7137.

March 24—**Ischemic Heart Disease—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 24-28—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 29-April 5—**Infectious Diseases.** Hilo, Hawaii. Saturday-Saturday. Naniloa and Kona Surf Hotels. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 31-April 3—**American College of Physicians: Hematology.** Seattle. Monday-Thursday. Olympic Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 3-4—**Hazards to the Fetus.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 8—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

April 10-11—**Dermatology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 10-11—**Annual Cancer Symposium—Gastrointestinal.** Seattle. Thursday-Friday. Swedish Hospital and Medical Center. Contact: John L. Wright, MD, Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

April 10-12—**Ninth Annual Refresher Course in Diagnostic Radiology.** Spokane. Thursday-Saturday. Sacred Heart Medical Center. Contact: Eunice Fisher, Department of Radiology, Sacred Heart Medical Center, West 101 8th Ave., TAF-C9, Spokane, WA 99220. (509) 455-3330.

April 12—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

April 15—**Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

April 17-18—**Couples.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 18-19—**Tacoma Surgical Society Annual Scientific Program.** Tacoma. Friday-Saturday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

April 24-25—**Respiratory Care.** Seattle. Thursday-Friday. Contract: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 24-25—**Review of Arrythmias.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 25-26—**Anesthesia: Low Flow States—Pathology and Treatment.** Vancouver, British Columbia. Friday-Saturday. Four Seasons Hotel. Contact: Dr. K. Turnbull, Academy of Medicine, 1807 West 10th Avenue, Vancouver, BC V6J 2A9.

April 28—**Cardiomyopathies and Pericardial Disease—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 1-2—**Controversies in Medicine.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 2-3—**Contemporary Clinical Neurology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 5—**Effective Alcoholism Treatment by General Physicians.** Seattle. Monday. Place to be announced. Copy of brochure available. Contact: Alcoholism Course, American Medical Society on Alcoholism, 733 Third Avenue, New York, New York 10017. (212) 986-4433.

May 5-6—**Patient-Physician Relationship.** Port Ludlow. Monday-Tuesday. The Admiralty. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 6—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Spokane). 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

May 8-10—**Washington Academy of Family Physicians—Annual Scientific Assembly.** Seattle. Thursday-Saturday. Red Lion Inn/Seattle-Tacoma Airport. 14 prescribed hours. Contact: Carolyn M. Palmer, Washington Academy of Family Physicians, 3700 140th Ave., NE, Bellevue, WA 98005. (206) 883-8852.

May 12—**Principles of Antibiotic Therapy—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 16-17—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 20—**Hypertension and Pregnancy—Univ. of Wash. OB-GYN Sessions** (Spokane). 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 22-23—**Adolescent Medicine.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 30—**Ophthalmology in Family Practice.** Seattle. Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 6-7—**Workshops in Musculoskeletal Disease.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Renal Disease.** Seattle. Thursday-Friday. Virginia

Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 19-20—**Laboratory Medicine.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 23—**Basic Concepts of Immunology and Their Application—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

June 26-27—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 28-July 5—**Alaska Cruise—Emergency Medical Care: Trauma, Orthopedics and Surgery; Biomedical History.** 8 days. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

July 25-26—**Seafair II Anesthesia Meeting**—Washington State Society of Anesthesiologists. Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Sandra McDonald, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

March 17-21

SPONSOR: University of Utah
TITLE: **Advances in Internal Medicine Conference**
LOCATION: Snowbird, Utah
FEE: $200
CREDIT: 22.5 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

March 18-20

SPONSOR: VA Regional Medical Education Center
TITLE: **Substance Abuse**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Steve Harmon (801) 582-1565, Ext. 1100

March 21

SPONSOR: Shriners Hospital for Crippled Children
TITLE: **18th Annual Scientific Session**
LOCATION: Shriners Hospital, Salt Lake City
FEE: To be announced
CREDIT: 12 hours
CONTACT: Grace Miya (801) 532-5307

March 21

SPONSOR: Hill Air Force Hospital
TITLE: **Emergency Transportation Problems and Abdominal Trauma**
LOCATION: HAFB Hospital Phys. Exam. Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

March 24-28

SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird, Utah
FEE: $200
CREDIT: 22.5 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

March 27-29

SPONSOR: Rocky Mountain Center for Occupational and Environmental Health/Harvard School of Public Health
TITLE: **2nd Annual Park City Environmental Health Conference**
LOCATION: Park City, Utah
FEE: Pending
CREDIT: 20 hours
CONTACT: Katharine Blosch (801) 581-7182

March 29

SPONSOR: Utah Heart Association
TITLE: **Scientific Session**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Florence Christensen (801) 322-5601

April 23-25

SPONSOR: VA Regional Medical Education Center
TITLE: **Heart Disease Update**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Lew Erschler (801) 582-1565, Ext. 1100

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UU: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-9, 1980, McKinley Village Lodge.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 23-27, 1980, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 24-27, 1980, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 13-17, 1980, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1980, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 2-4, 1980, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 16-18, 1980, MGM Grand, Las Vegas.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 7-9, 1980, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-31, 1980, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 30-October 3, 1980, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 2-5, 1980, Thunderbird at Jantzen Beach, Vancouver, WA.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 23-27, 1980, Snow King Inn, Jackson.

May 13-15
SPONSOR: VA Regional Medical Education Center
TITLE: **Substance Abuse**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Steve Harmon (801) 582-1565, Ext. 1100

June 16-20
SPONSOR: VA Regional Medical Education Center
TITLE: **Legal Medicine**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Lew Erschler (801) 582-1565, Ext. 1100

August 26-28
SPONSOR: VA Regional Medical Education Center
TITLE: **Conflict, Confrontation, and Stress**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Alan Lundgren (801) 582-1565, Ext. 1100

September 22-25
SPONSOR: VA Regional Medical Education Center
TITLE: **Sexual Health**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: George Keiser, PhD (801) 582-1565, Ext. 1100

October 1-2
SPONSOR: VA Regional Medical Education Center
TITLE: **Geriatric Assessment**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Barbara Cordell, RN (801) 582-1565, Ext. 1100

October 16
SPONSOR: LDS Hospital (with Intermountain Thoracic Society, Utah Heart Association and University of Utah)
TITLE: **Postgraduate Course—Pulmonary Heart Disease**
LOCATION: LDSH
FEE: To be announced
CREDIT: 6 hours
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

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★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the Utah State Medical Association and the Washington State Medical Association**

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Dalmane (flurazepam HCl/Roche) induced sleep within 17 minutes, on average, in 32 insomniac subjects during short-term evaluation in the sleep laboratory. The subjects averaged 7 to 8 hours of sleep.[1] Moreover, the sleep latency (time required to fall asleep) of 5 insomniacs receiving Dalmane for a longer period of time averaged only 17.7 minutes throughout 28 consecutive nights of administration, with an average of 7.1 hours of sleep.[2]

EFFICACY FOR A GREATER NUMBER OF NIGHTS
Patients obtained relief for at least 28 consecutive nights

Dalmane (flurazepam HCl/Roche) is the only sleep medication objectively tested and proved effective for a 4-week period.[2,3] Because insomnia is usually transient, the prolonged administration of any sleep medication is seldom necessary. Should Dalmane be used for a prolonged period, the appropriate patient evaluations such as periodic blood counts and liver and kidney function tests should be performed.

A BETTER SAFETY PROFILE THAN MOST SLEEP MEDICATIONS

A wider margin of safety[1]

Dalmane (flurazepam HCl/Roche) offers a safety profile comparably higher than many other sleep medications. There have been no reports of physical or psychological dependence when taken at recommended dosages. In controlled studies involving 2115 patients, the majority of side effects reported were of the sedative-type generally expected with a sleep medication. As with all medications in its class, Dalmane should be administered with caution to patients who are addiction-prone. Patients should also be cautioned about possible combined effects with alcohol and other CNS depressants.

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flurazepam HCl/Roche

30-MG AND 15-MG CAPSULES

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Please see next page for a summary of product information.

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Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies, or with impaired renal or hepatic function. Periodic blood counts and liver and kidney function tests are advised during repeated therapy.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, e.g. excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients.
Elderly or debilitated patients: 15 mg **recommended** initially until response is determined.
Supplied: Capsules containing 15 mg (orange and ivory); or 30 mg (red and ivory) flurazepam HCl.

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One 30-mg capsule *h.s.*—usual adult dosage
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One 15-mg capsule *h.s.*—recommended initial dosage for elderly or debilitated patients.

REFERENCES:
1. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
2. Dement WC, *et al*: *Behav Med* 5:25-31, Oct 1978
3. Kales A, *et al*: *Clin Pharmacol Ther* 19:576-583, May 1976

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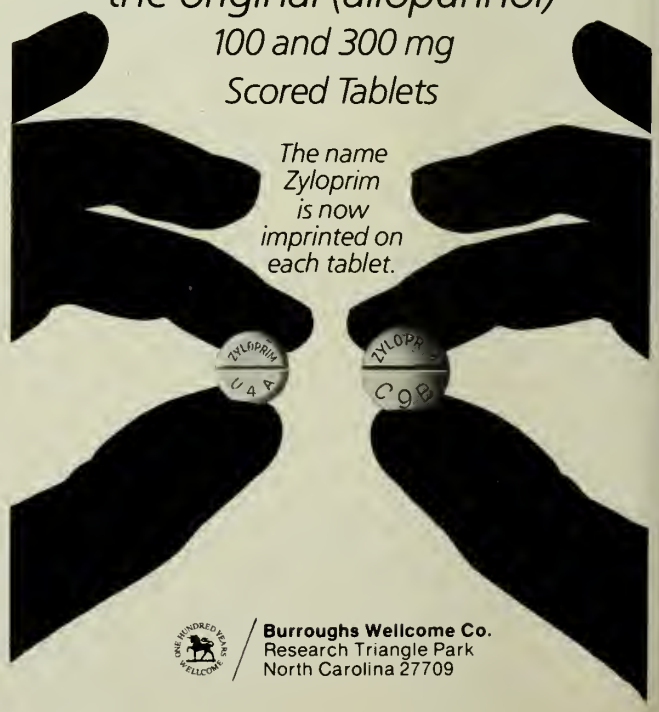

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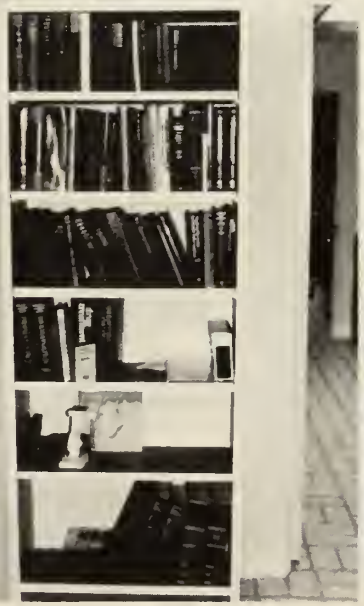

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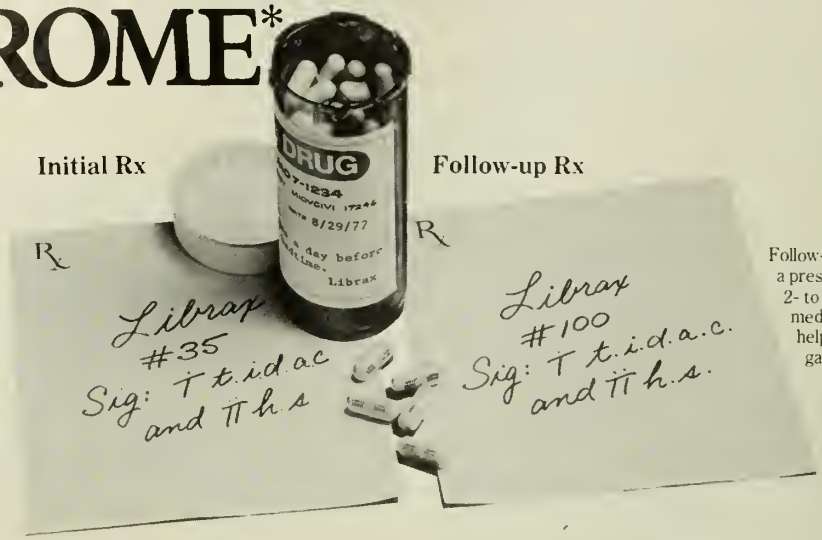

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As with all anticholinergics, inhibition of lactation may occur.

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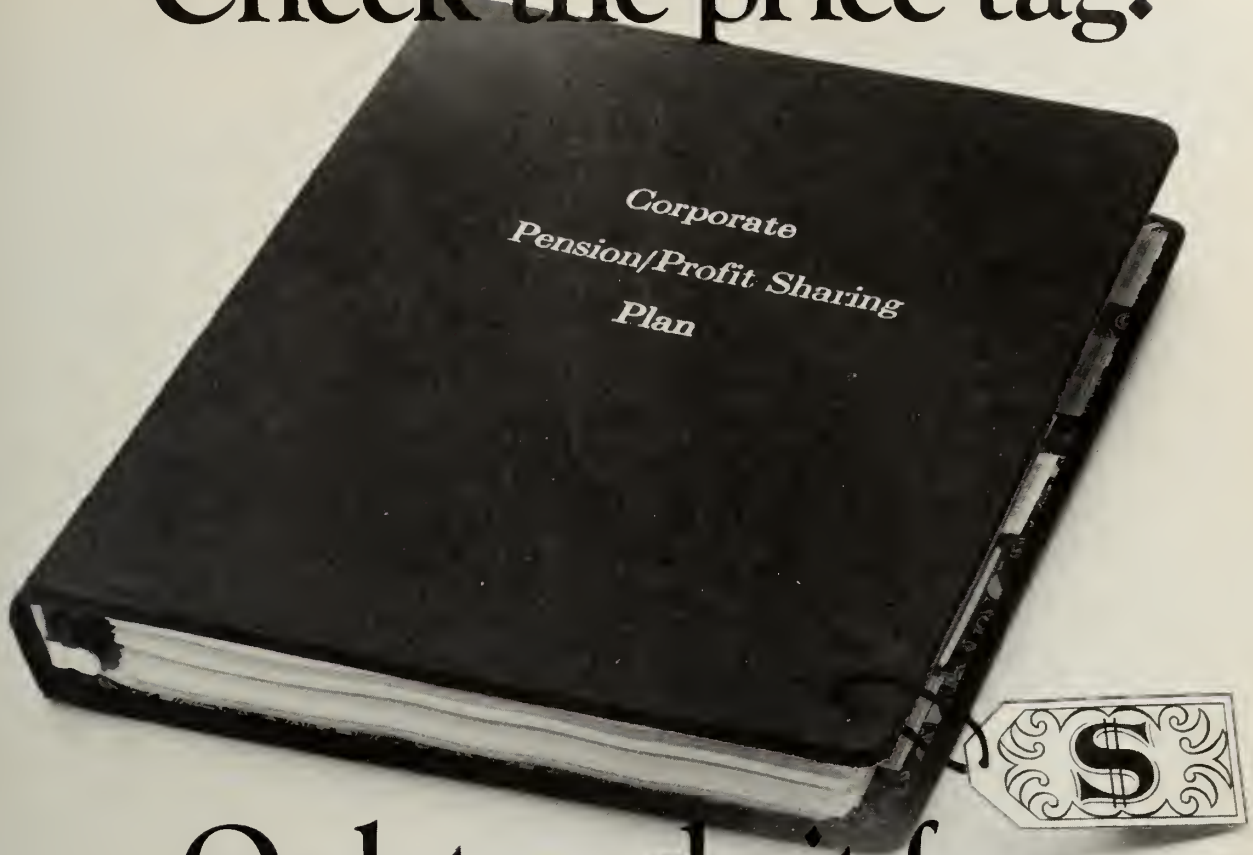

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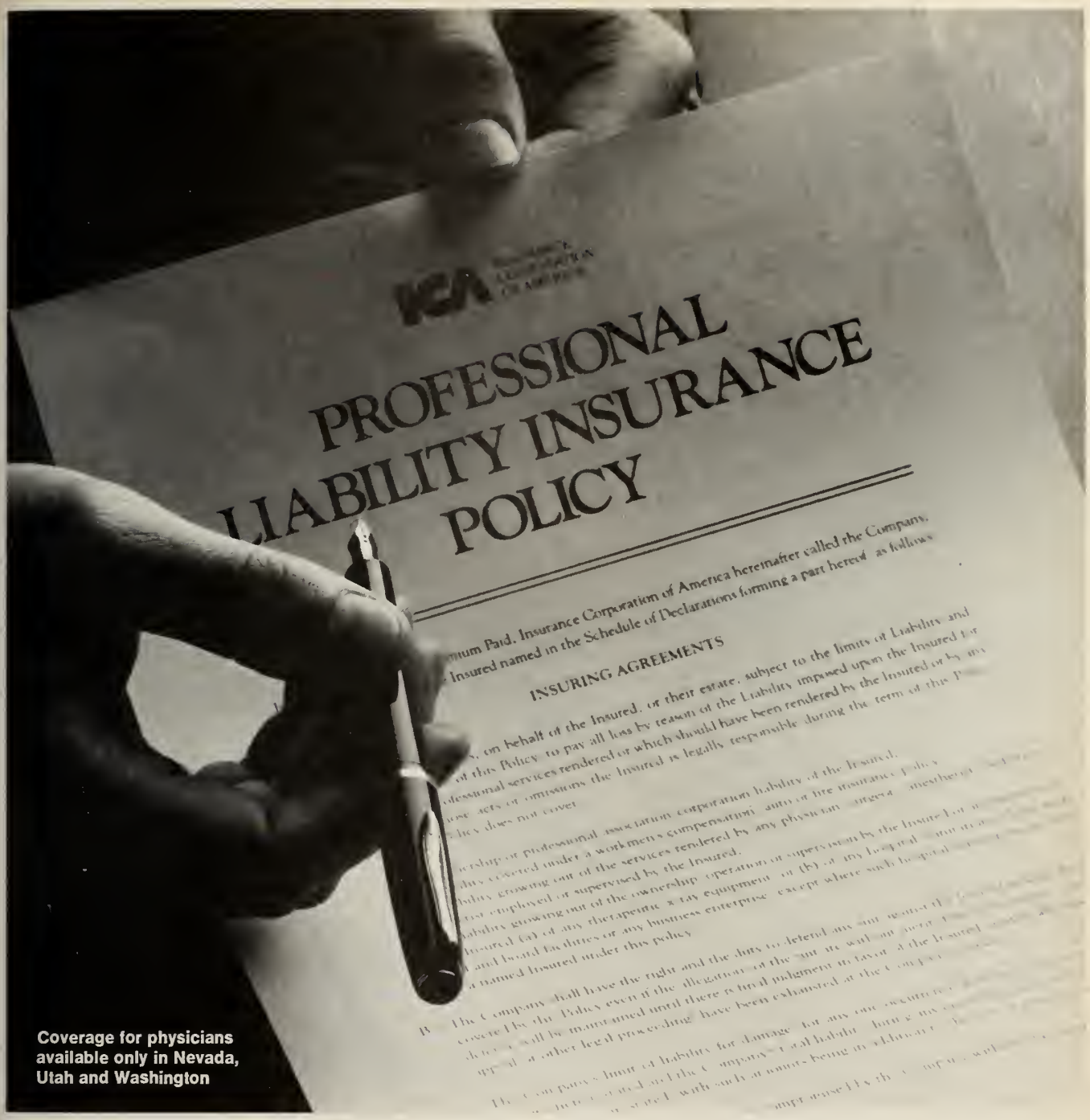

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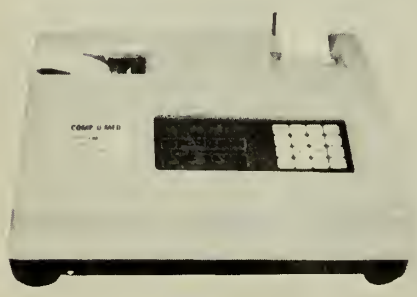

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Refer to: Wasnich RD, Puapongsakorn R, Seto DSJ: Significance of antibody to hepatitis B core antigen in a hemodialysis unit. West J Med 132:279-282, Apr 1980

Significance of Antibody to Hepatitis B Core Antigen in a Hemodialysis Unit

RICHARD D. WASNICH, MD; RATANA PUAPONGSAKORN, MD, *and*
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Serum hepatitis B surface antigen (HB_sAg), antibody to HB_sAg (anti-HB_s) and antibody to hepatitis B core antigen (anti-HB_c) were determined serially in patients and staff in a hemodialysis unit. A low prevalence of HB_sAg (2.8 percent) was found. However, in patients without HB_sAg, anti-HB_c alone was present in 9.2 percent, and coexistent anti-HB_s and anti-HB_c in 19.2 percent. In persons with anti-HB_c only, the levels of anti-HB_c correlate positively with abnormal results on liver function studies (LFS). In all subjects with abnormal LFS findings, anti-HB_c levels were greater than 6.04 radioimmunoassay (RIA) units. In subjects with both anti-HB_s and anti-HB_c, all five subjects with higher anti-HB_c relative levels had abnormal LFS results and all subjects with normal LFS results had higher anti-HB_s relative levels. Along with other recent reports in the literature, these findings suggest a hepatitis B prevalence in this hemodialysis unit far in excess of that anticipated on the basis of HB_sAg prevalence.

HEPATITIS B remains a significant problem for both patients and personnel in renal dialysis units. A 1973 survey of 15 hemodialysis units found a serum hepatitis B surface antigen (HB_sAg) prevalence of 16.8 percent in patients and 2.4 percent in staff.[1] Other patients and personnel are easily exposed to this reservoir of chronic antigenemia. However, recent studies of hepatitis B core antigen (HB_cAg) and antibody to HB_cAg (anti-HB_c) indicate that the reservoir of chronic hepatitis B may be significantly larger than suspected on the basis of HB_sAg prevalence.[2,3] Because of the importance of accurately identifying hemodialysis patients capable of transmitting hepatitis B, we have undertaken measurements of HB_sAg, antibody to HB_sAg (anti-HB_s) and anti-HB_c in all hemodialysis patients and staff.

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Submitted, revised, September 19, 1979.
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Materials and Methods

Measurement of HB_sAg was made by solid phase radioimmunoassay (RIA) (Ausria II, Abbot Laboratories, North Chicago, Illinois). Anti-HB_s was also measured by solid phase radioimmunoassay (Ausab, Abbott Laboratories). Results of both procedures are expressed as a ratio of sample counts per minute to a negative control mean counts per minute. Any sample yielding a ratio greater than 2.1 is considered positive. Anti-HB_c was tested for by a solid-phase competitive-

ABBREVIATIONS USED IN TEXT
anti-HB_c = antibody to HB_cAg
anti-HB_s = antibody to HB_sAg
HB_cAg = hepatitis B core antigen
HB_sAg = hepatitis B surface antigen
HBV = hepatitis B virus
LFS = liver function studies
RIA = radioimmunoassay

inhibition radioimmunoassay (Corab, Abbott Laboratories). A cutoff value is determined by the following formula:

$$\frac{NCx + PCx}{2} = \text{cutoff value}$$

NCx is the negative control mean and PCx is the positive control mean. Samples having counts equal to or less than the cutoff value are considered positive. Estimation of anti-HB_c was arbitrarily expressed by the following formula:

$$\frac{NCx}{\text{sample Cx}} = \text{RIA units}$$

All anti-HB_s and anti-HB_c results have been confirmed by repeat testing. HB_sAg results have been confirmed by specific inhibition testing.

Results

Hemodialysis patient and employee results are shown in Table 1. Four patients possess HB_sAg and have been identified as HB_sAg carriers on serial examinations. None of 33 employees is positive for HB_sAg. Except for this difference in HB_sAg prevalence between patients and employees, there are no differences in the distributions and prevalences of anti-HB_s and anti-HB_c. A total of 51 subjects are positive for anti-HB_c, including the 4 patients positive for HB_sAg. Of these 51 subjects, 15 (designated group A) possess anti-HB_c in the absence of either anti-HB_s or HB_sAg. Another 32 (designated group G) are positive for both anti-HB_c and anti-HB_s, but negative for HB_sAg.

The results of liver function studies in group A are shown in Table 2. Any subject in whom a bilirubin, alkaline phosphatase or serum glutamic pyruvic transaminase value is abnormal is listed as having abnormal liver function. In 14 of the 15 group A subjects, results of liver function studies (LFS) are available; in four, liver function is normal and in the remaining ten LFS results are abnormal. When compared with the anti-HB_c level, all four subjects with normal LFS findings have ratios less than 4.68, whereas nine of ten subjects with abnormal LFS results have ratios greater than 6.04. The tenth subject has since become negative for anti-HB_c and LFS results have returned to normal.

A similar analysis of group G is shown in Table 3. The results of anti-HB_s and anti-HB_c determinations have been expressed as an anti-HB_s/anti-HB_c ratio. This ratio does not reflect the absolute levels of anti-HB_s and anti-HB_c, since the two assays may have different sensitivities. However, for the particular assays employed, a ratio less than 1.0 indicates a relative anti-HB_c level greater than the anti-HB_s level, and a ratio greater than 1.0 indicates that the relative anti-HB_s level exceeds the anti-HB_c level. Of 33 subjects in group G, LFS findings are available in 30. In 12, LFS results were normal, and all 12 have anti-HB_s/anti-HB_c ratios greater than 1.0, with a mean ratio of 7.22. All five subjects with anti-HB_c levels exceeding anti-HB_s levels have abnormal LFS results. The remaining 13 have abnormal LFS results and anti-HB_s/anti-HB_c levels greater than 1.11 (mean 7.91).

Discussion

Despite the implementation of more stringent hepatitis B control procedures in hemodialysis units, transmission of the disease remains a significant risk for both patients and staff.[1,4] Although the prevalence of hepatitis B carriers appears to be higher in Hawaii than on the United

TABLE 1.—*Classification According to Hepatitis B Test Results*

Group	*Anti-HB_c*	*HB_sAg*	*Anti-HB_s*	*Patients (%)*	*Employees (%)*	*Total (%)*
A	+	−	−	13 (9.2)	2 (6.1)	15 (8.6)
B	+	+	−	3 (2.1)	0 (0.0)	3 (1.7)
C	+	+	+	1 (0.7)	0 (0.0)	1 (0.6)
D	−	−	−	87 (61.7)	23 (69.7)	110 (63.2)
E	−	+	+	0 (0.0)	0 (0.0)	0 (0.0)
F	−	−	+	10 (7.1)	3 (9.1)	13 (7.5)
G	+	−	+	27 (19.2)	5 (15.2)	32 (18.4)
TOTAL .				141 (100.0)	33 (100.0)	174 (100.0)

States mainland,[5,6] the 2.8 percent prevalence of HB_sAg carriers in our hemodialysis unit appears to be paradoxically low. In contrast, anti-HB_c is present in 31.7 percent of patients; significantly, 9.2 percent of patients possess anti-HB_c in the absence of anti-HB_s or HB_sAg.

The presence of anti-HB_s indicates previous exposure to hepatitis B virus, and it is generally considered to represent recovery and immunity to reinfection.[8] Hemodialysis patients and staff have anti-HB_s prevalences of 26.9 percent and 24.2 percent, respectively. Anti-HB_c, in contrast to anti-HB_s, appears during the acute phase of the illness, and it may persist long after anti-HB_s has disappeared.[3,7] Although anti-HB_c has long been considered to reflect continuing hepatitis B virus (HBV) replication,[2] its significance as a marker of potential infectivity has only recently been appreciated. Hoofnagle and co-workers[3] have shown that blood units containing anti-HB_c, but containing no detectable HB_sAg, are capable of transmitting hepatitis B to blood recipients.

Omata and associates have also shown that 100 percent of their patients positive for anti-HB_c, but negative for anti-HB_s and HB_sAg, have tissue HB_cAg present in autopsy liver specimens.[9] Thus group A in our study, representing 9.2 percent of patients and 6.1 percent of staff, would be considered to have continuing HBV replication in the liver and would also be considered as potentially infectious. We have found that 71.4 percent of our group A subjects have abnormal LFS results. Significantly, all four group A subjects with normal findings on LFS have anti-HB_c levels less than 4.68 RIA units, whereas nine of ten subjects with abnormal LFS results have anti-HB_c levels greater than 6.04 RIA units. The tenth subject with abnormal results on LFS, and an original anti-HB_c level of 2.18 RIA units, has since become negative for anti-HB_c and results on LFS returned to normal. Subsequent testing for anti-HB_s has also been negative.

Although definitive proof of hepatitis B in group A is lacking, these findings are quite compatible with the findings of Omata and co-workers. The presence of high titers of anti-HB_c, in the absence of anti-HB_s, correlates uniformly with abnormal results on liver function studies. Based upon current evidence, these subjects must be considered highly suspect as hepatitis B carriers. Significantly, there are 13 patients and 2 employees in this category, as opposed to only 4 patients with HB_sAg. Thus if these findings are confirmed, the actual prevalence of hepatitis B in our hemodialysis unit is significantly greater than previously suspected. Although this figure is surprisingly high, it is in agreement with our data on 50 donor blood units.[5] Although all donors were negative for HB_sAg, 12 percent had anti-HB_c, and 10 percent had anti-HB_c in the absence of anti-HB_s. The implications for the future control of hepatitis B are apparent.

A more difficult diagnostic problem is presented by group G subjects, who represent 19.2 percent of patients and 15.2 percent of employees. These subjects possess both anti-HB_s and anti-HB_c. Of considerable significance is Omata's finding that the coexistence of anti-HB_s and anti-HB_c does not indicate immunity, since two of five such patients in his study had HB_cAg in their livers. Although Omata has confirmed that the presence of anti-HB_s only (group F in our series) is indicative of immunity, he has shown that high titers of anti-HB_c, even with the coexistence of anti-HB_s, are indicative of HBV replication in the liver.

For purposes of hepatitis B control in a hemodialysis unit, it must therefore be presumed that a significant proportion of group G subjects, perhaps as high as 40 percent, are also infectious for

TABLE 2.—*Comparison of Liver Function Study (LFS) Results and Anti-HB_c Levels*

Normal LFS Results	*Abnormal LFS Results*	*Anti-HB_c (RIA units)*	*Patients*	*Employees*	*Total*
4	..	1.36- 4.68	2	2	4
..	9	6.04-42.69	9	..	9
..	1	2.18	1	..	1

TABLE 3.—*Comparison of Liver Function Study (LFS) Results and Anti-HB_s/Anti-HB_c Ratios*

Normal LFS	*Abnormal LFS*	*Anti-HB_s/Anti-HB_c Ratio*	*Patients (%)*	*Employees (%)*	*Total (%)*
12	..	1.04-15.52 (M=7.22)	9 (34.6)	3 (75)	12 (40.0)
..	5	0.36- 0.88 (M=0.66)	4 (15.4)	1 (25)	5 (16.7)
..	13	1.11-41.47 (M=7.91)	13 (50.0)	0	13 (43.3)
12	18		26 (100.0)	4 (100)	30 (100.0)

hepatitis B. The clinical dilemma is to determine which of these subjects are infectious and which are immune. When LFS results are considered in group G, 60.0 percent are abnormal (Table 3). If the relative levels of anti-HB_s and anti-HB_c are expressed as an anti-HB_s/anti-HB_c ratio, all 12 subjects with normal findings on liver function studies have ratios greater than 1.04, indicating relative anti-HB_s levels greater than anti-HB_c levels. Only five group G subjects have anti-HB_c levels greater than anti-HB_s levels, and in all five, LFS results are abnormal. An additional 13 subjects with abnormal LFS results have anti-HB_s/anti-HB_c ratios greater than 1.0.

The five subjects with high anti-HB_c levels and abnormal LFS findings are the most suspect for hepatitis B. Unfortunately, only liver biopsy with immunofluorescent staining for HB_cAg and HB_sAg can definitely establish the diagnosis, and this involves risk when applied to large numbers of patients with hemorrhagic tendencies. Quantitative liver-spleen scintigraphy is an alternative, noninvasive method for the detection of hepatocellular disease.[10] Although nonspecific, it may be helpful in selection of patients in whom biopsy is required. Further studies employing this technique in the group G subjects are in progress.

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Propranolol Versus Coronary Bypass for Angina Pectoris

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* * * * *

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—SHAHBUDIN H. RAHIMTOOLA, MD, *Portland, Oregon*
—J. DAVID BRISTOW, MD, *San Francisco*

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Refer to: Freeny PC, Kidd R, Ball TJ: ERCP-guided percutaneous fine-needle pancreatic biopsy. West J Med 132:283-287, Apr 1980

ERCP-Guided Percutaneous Fine-Needle Pancreatic Biopsy

PATRICK C. FREENY, MD; REILEY KIDD, MD, *and* TERRENCE J. BALL, MD, *Seattle*

In patients with a radiologic diagnosis of unresectable pancreatic carcinoma, exploratory laparotomy for tissue diagnosis is no longer required. Histologic confirmation of the diagnosis may be obtained safely and accurately with percutaneous fine-needle aspiration biopsy. Endoscopic retrograde cholangiopancreatography (ERCP) precisely localized the biopsy site for cytologic diagnosis of adenocarcinoma in 13 of 14 patients (93 percent) with pancreatic carcinoma.

DIAGNOSIS AND TREATMENT in cases of carcinoma of the pancreas continue to be a challenge.[1] Most patients with pancreatic carcinoma are found to have incurable tumors at the time of initial presentation.[2,3] While palliative bypass surgical operations are required in those cases of pancreatic carcinoma with secondary obstruction of the biliary tree, patients with a radiologic diagnosis of unresectable pancreatic carcinoma continue to undergo exploratory laparotomy carried out only for confirmation of the radiologic diagnosis or for obtaining tissue for histologic examination.[3]

In the latter group, histologic verification of carcinoma of the pancreas can be obtained without the morbidity and expense of laparotomy by percutaneous fine-needle aspiration biopsy.[4-9] This paper describes our experience with this technique in 14 cases, using endoscopic retrograde cholangiopancreatography (ERCP) for localization of the biopsy site.

Patients and Methods

In 14 nonjaundiced patients with suspected pancreatic carcinoma, diagnostic evaluations were carried out using a combination of ultrasonography or computed tomography, endoscopic retrograde cholangiopancreatography, angiography and percutaneous fine-needle pancreatic biopsy.[2] Of the patients, seven were men and seven were women, with ages ranging from 55 to 82 years (average 68 years). In each of the patients an ERCP diagnosis of pancreatic carcinoma was made, and subsequent angiography in each indicated that the tumors were unresectable.

Percutaneous fine-needle aspiration biopsy of the tumors was done at the conclusion of arteriography in each case. Informed consent for the biopsy procedure was obtained from the patients before arteriography. Patient preparation and premedication were the same as those used for the arteriography: no solid food for 8 to 12 hours and diazepam (Valium), 10 mg given orally. Following the biopsy and arteriography, the postprocedural orders included bed rest for six hours and close monitoring of vital signs for four hours.

Biopsy Procedure

Tray setup. A simple tray setup is used for the biopsy procedure (Figure 1). The tray contains povidone-iodine (Betadine) swabs, 1 percent lidocaine (Xylocaine) solution for local anesthesia, a

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Submitted, revised, August 17, 1979.

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20-cm 23-gauge stainless steel needle with a 30 degree bevel (Cook, Inc., Bloomington, Indiana), a 12-ml syringe, ground glass slides and spray fixative.

Tumor Localization. The supine (anteroposterior) films from the ERCP are used to locate the site of the obstructed or encased pancreatic duct. Ultrasonography or computed tomography may be used to estimate the distance from the skin to the center of the pancreatic mass.

Aspiration Procedure. The skin is prepared with povidone-iodine, the abdominal wall is infiltrated with 1 percent lidocaine solution for local anesthesia and a small stab incision is made in the skin. In large patients, an 18-gauge needle is inserted through the skin and subcutaneous tissues as a guide for the biopsy needle. The patient is asked to hold his breath and the 23-gauge needle is advanced perpendicularly to the proper location using television-monitored fluoroscopic control. A firm, gritty sensation is usually felt as the needle enters the tumor. The stylet is then removed from the needle and a 12-ml syringe is attached to the hub. Continuous maximum suction is applied while the needle is both rotated and moved up and down 1 to 2 cm (Figure 2). Suction is then released, the needle removed and the patient instructed to breath normally.

Cytology Preparation. Initially, only a single biopsy specimen is taken. Part of the aspirate is smeared on ground glass slides and immediately sprayed with a fixative. The remainder of the material is placed in preservative media for centrifugation and preparation of a cell block. The cytologist, who is in attendance during the procedure (usually about ten minutes), immediately stains the slides with a commercial preparation (Diff-Quick, Harleco, Gibbstown, New Jersey)

Figure 1—Pancreatic biopsy tray setup. Tray consists of sterile towels, povidone-iodine (Betadine) swabs, 1 percent lidocaine (Xylocaine), No. 11 blade, syringes, ground glass slides, spray fixative, bowl of sterile saline, and a 20-cm 23-gauge stainless steel needle for biopsy.

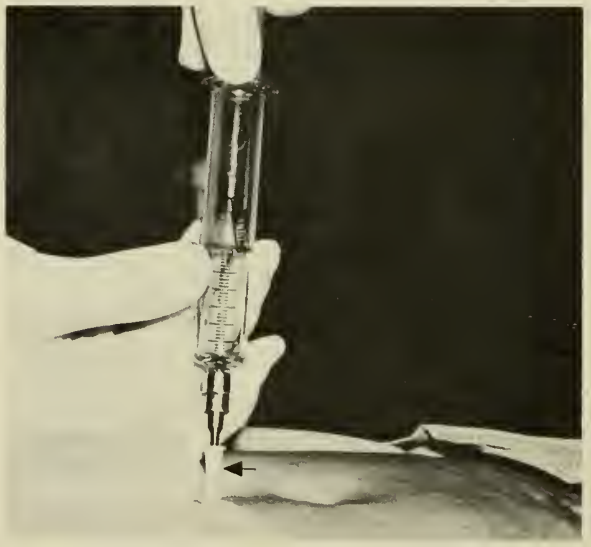

Figure 2.—Needle placement. The 23-gauge biopsy needle is attached to a 12-ml glass syringe. Continuous maximum suction is applied as the needle is rotated and moved up and down. An 18-gauge needle is inserted through the skin and subcutaneous tissues for a guide (arrow).

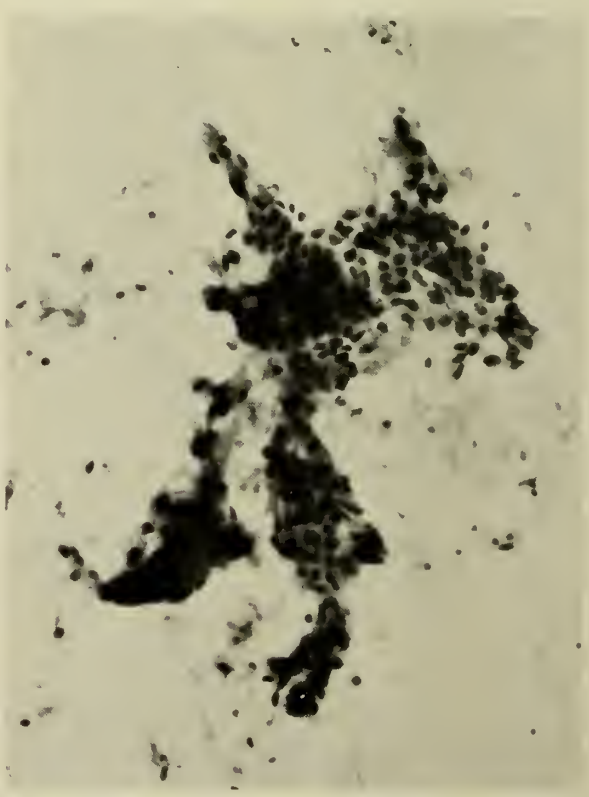

Figure 3.—Cytology. Typical pleomorphic cells of adenocarcinoma obtained by aspiration biopsy.

similar to Wright-Giemsa stain (Figure 3). These are taken directly to the cytology laboratory and the results are available within 10 to 15 minutes. If the results are positive, no further biopsy specimens are taken. If the results are negative or equivocal, the cytologist returns to the fluoroscopic suite and an additional specimen is obtained.

Results

In each of the 14 patients an ERCP diagnosis of pancreatic carcinoma was made using criteria described in previous reports.[10,11] The pancreatic duct was obstructed in 13 cases and encased in 1 case. The malignant lesions were located in the uncinate process (one case), head and body (three cases), body (seven cases) and tail (three cases) of the pancreas.

The angiographic findings indicated unresectable carcinoma in each case. The criteria used to assess resectability included tumor involvement of major extrapancreatic vascular structures, contiguous organ invasion and hepatic metastatic lesions.[12-16]

Percutaneous fine-needle pancreatic biopsy was done in each patient following the arteriographic diagnosis of unresectable pancreatic carcinoma. The biopsy findings were positive for adenocarcinoma in 13 of the 14 patients. In only one of the 14 patients was laparotomy required. In this patient, only a few reactive cells were obtained despite two biopsy attempts. The diagnosis was confirmed by results of surgical biopsy.

In two patients a course of chemotherapy was started; they died three and four months following diagnosis. The remaining 11 patients expired from 1 to 8 months (average 3.4 months) following diagnosis. The radiologic findings, positive aspiration biopsy findings and subsequent clinical courses of each of these patients were accepted as confirmation of the diagnosis of pancreatic carcinoma.

The only pain caused by the biopsy procedure was related to the temporary discomfort of lidocaine infiltration of the abdominal wall. No complications occurred in this series as a result of either the initial diagnostic examinations or the biopsy procedures. No significant complications have been reported by other investigators using this technique.[4-9] Goldstein and associates carried out experimental biopsies on laboratory animals. Inspection of the biopsy sites immediately and 46 hours later showed no significant findings.

TABLE 1.—*Percutaneous Fine-Needle Pancreatic Biopsy of Pancreatic Carcinoma*

Author	*No. of Cases*	*Correct (%)*	*Localization*
Smith[4]	6	5 (83)	us
Hancke[5]	21	17 (81)	us
Tylen[6]	29	22 (76)	angio
Goldstein[7]	34	25 (73)	us; angio; BE
Goldman[8]	11	6 (55)	us; angio; BE; PTC
McLoughlin[9] ..	18	16 (89)	ERCP; angio; PTC; BE
Freeny	14	13 (93)	ERCP; angio; us
TOTAL	133	104 (78.2)	

us = ultrasonography; angio = angiography; BE = barium examination; PTC = percutaneous transhepatic cholangiography; ERCP = endoscopic retrograde cholangiopancreatography.

In most cases, there was no observable evidence of needle passage.[7]

Discussion

Essentially all patients with carcinoma of the body or tail of the pancreas have incurable tumors by the time they present for radiologic evaluation. While occasionally a tumor can be resected, this is done with high morbidity and mortality. Average survival following diagnosis is only 6 to 12 months.[1,2] The potential morbidity, discomfort and expense of any procedures carried out following the radiologic diagnosis of unresectable tumor must be important considerations for both patient and physician. However, as stated by Gudjonsson and Spiro, "whatever therapeutic methods the physician considers appropriate, the therapy of pancreatic cancer demands histological evidence."[3] Percutaneous fine-needle pancreatic biopsy is to be contrasted with a surgical procedure done only to confirm the radiologic diagnosis and to obtain histologic proof of diagnosis. In this series, there was no morbidity, and the cost and discomfort of surgical operation was avoided in all but one patient.

Our current approach is to use either ultrasonography or computed tomography for initial evaluation in patients with suspected pancreatic carinoma.[2] If either of these modalities identifies a pancreatic mass with associated liver or nodal metastatic lesions, a diagnosis of unresectable pancreatic carcinoma is made and a percutaneous biopsy study is done using either the ultrasonogram or a computed tomogram for guidance. If only an isolated pancreatic mass is identified, ERCP is then carried out for specific diagnosis of inflammatory or neoplastic disease. If the ERCP diagnosis is tumor, angiography is used to de-

termine resectability and biopsy specimens of unresectable tumors are taken using the ERCP for guidance.[2,11]

Two factors influence the accuracy of pancreatic biopsy: (1) localization of the biopsy site and (2) interpretation of the cytology specimen. Previous reports have established that similar results may be obtained using any of the available imaging procedures for localization.[4-9] Accuracy ranges from 55 percent to 89 percent (Table 1).

With the exception of using ERCP to determine the precise biopsy site, our techniques were no different than those of other investigators. We obtained a positive cytologic diagnosis in 13 of 14 patients (93 percent). We feel that ERCP is the most accurate method for biopsy localization because most pancreatic carcinomas arise from the ductal epithelium.[17] Therefore, the site of pancreatic duct obstruction or encasement is the site of the tumor. Much of the mass seen by ultrasonography or computed tomography and some of the vascular changes seen on angiograms are due to a rim of pancreatitis surrounding the tumor.[12,18] Biopsy of this area yields normal or inflamed cells and results in a false negative cytologic finding. In fact, it appears that the larger the mass, the more likely that the biopsy results will be inconclusive.[7] If ERCP is available and has been used for initial diagnostic evaluation, our experience suggests that it is the most accurate method for biopsy localization (Figure 4). However, if the initial diagnosis of unresectable pancreatic carcinoma is made by ultrasonography or computed tomogra-

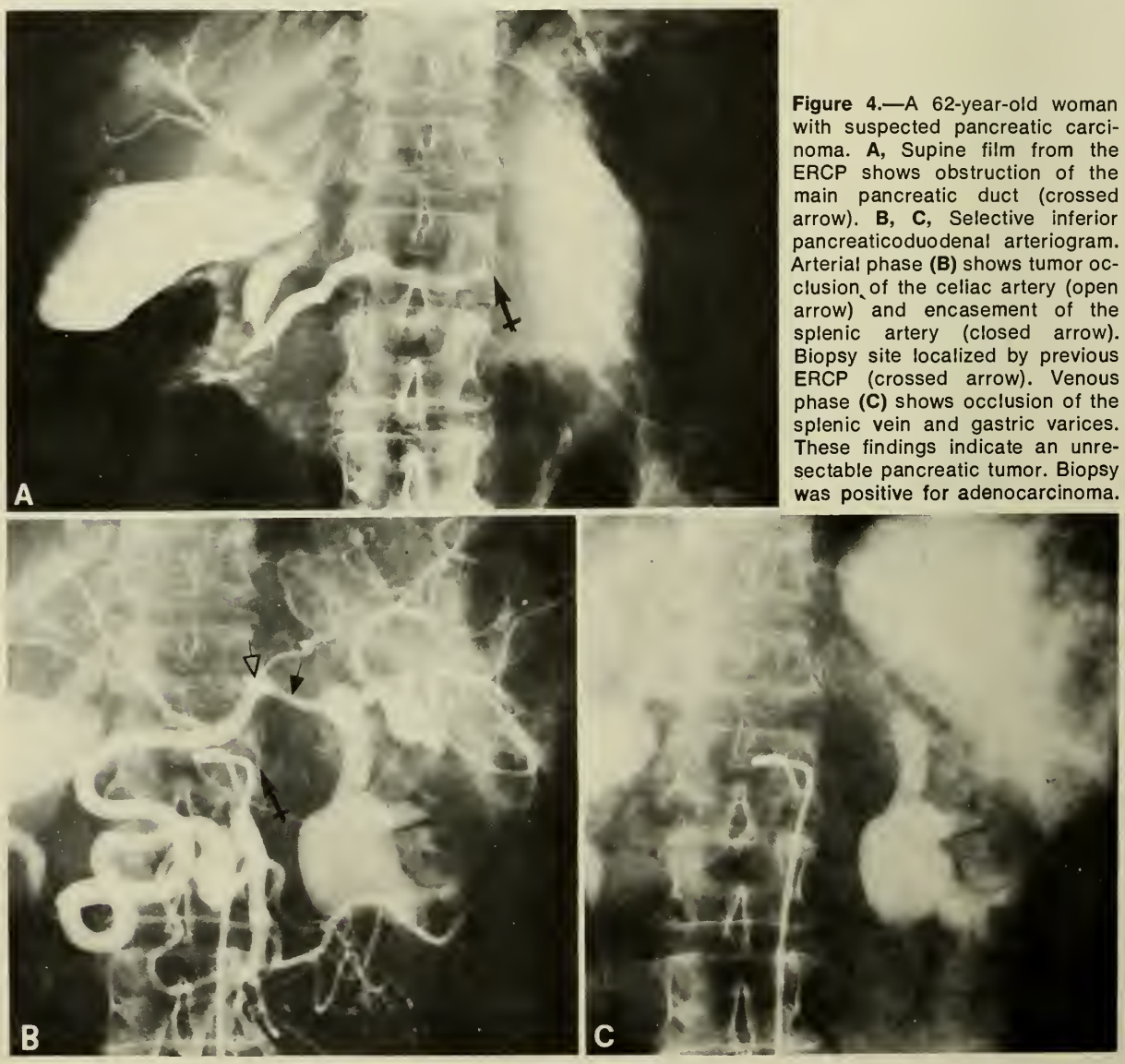

Figure 4.—A 62-year-old woman with suspected pancreatic carcinoma. **A,** Supine film from the ERCP shows obstruction of the main pancreatic duct (crossed arrow). **B, C,** Selective inferior pancreaticoduodenal arteriogram. Arterial phase **(B)** shows tumor occlusion of the celiac artery (open arrow) and encasement of the splenic artery (closed arrow). Biopsy site localized by previous ERCP (crossed arrow). Venous phase **(C)** shows occlusion of the splenic vein and gastric varices. These findings indicate an unresectable pancreatic tumor. Biopsy was positive for adenocarcinoma.

phy, these modalities are used for guidance for percutaneous biopsy. If negative results are obtained, then ERCP may be carried out for further diagnosis and for guidance for subsequent biopsy.

Expert cytopathologic support is mandatory for obtaining reliable diagnoses. Standard slide and cell block preparation, staining and cytological interpretation techniques are used.

We have not done percutaneous pancreatic biopsies in patients who are jaundiced or who have intestinal involvement and thus require palliative surgical bypass procedures, or in patients in whom the arteriogram indicates a resectable tumor. In the first group of patients, tumor resectability and histologic diagnosis may be determined at the time of surgical operation. In the second group, we feel that a biopsy study should not be done if resection is contemplated. A previous report on the accuracy of preoperative ERCP-guided biopsy has been published.[9,19] However, tumor resectability was not investigated before biopsy and we can not recommend this approach. Although the potential of needle tract seeding of tumor is low, a case has been reported.[20] Because so very few pancreatic carcinomas are resectable, we do not feel that even a minimally increased risk of tumor dissemination is acceptable.

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Mixed Connective Tissue Disease

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A study was done that involved 46 patients with high-titer serum antibody to ribonucleoprotein (RNP). Common cutaneous manifestations included swollen hands or sclerodactyly (50 percent), cutaneous lupus erythematosus (48 percent), periungual telangiectasia (46 percent), alopecia (46 percent), dyspigmentation (28 percent), photosensitivity (28 percent) and vasculitis (22 percent). Frequent systemic characteristics included Raynaud phenomenon (93 percent), arthritis or arthralgia (91 percent), adenopathy (43 percent), vascular headaches (35 percent), serositis (35 percent), hoarseness (28 percent), myositis (26 percent), sicca syndrome (24 percent), renal disease (17 percent) and central nervous system disease (9 percent). Associated laboratory findings included antinuclear antibodies (100 percent), epidermal nuclear IgG deposition (91 percent), hypergammaglobulinemia (78 percent), esophageal dysmotility (61 percent), abnormal pulmonary function (59 percent), rheumatoid factor (57 percent), lupus erythematosus cells (37 percent), positive lupus band test (34 percent), hypocomplementemia (28 percent) and elevated anti-nDNA (21 percent).

It appears that patients with high-titer anti-RNP (without appreciable amounts of "anti-Sm") have a high prevalence of Raynaud phenomenon and a low prevalence of progressive renal insufficiency and severe central nervous system disease.

In 1972, Sharp and co-workers[1] described a group of patients designated as having mixed connective tissue disease (MCTD) with benign features often compatible with systemic lupus erythematosus (SLE), but suggestive of scleroderma or polymyositis, or both. Serum antibody to a ribonuclease-sensitive extractable nuclear antigen (ENA) termed anti-RNP is, by definition, the immunologic marker of this connective tissue disease subset. This paper expands the ribonucleoprotein (RNP) spectrum of connective tissue disease to a patient population more representative of private practice than of referral centers.

Patients and Methods

The only criterion for patient selection was the presence of serum antibody in high titer (mean = 1:149,200) to ribonucleoprotein. Forty-six patients were examined by the author on one or more occasions and comprehensive studies carried out using a pretested clinical research protocol. Of the patients, 39 were women and

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ABBREVIATIONS USED IN TEXT

ANA = antinuclear antibody
ENA = extractable nuclear antigen
LE = lupus erythematosus
MCTD = mixed connective tissue disease
RNase = ribonuclease
RNP = ribonucleoprotein

7 were men (sex ratio, 5.6:1). Thirty-two patients were white, seven were black and seven were Oriental. The black and Oriental patients were all women. Ages ranged from 9 to 53 years, with a mean age of 36. The presence or absence of the cutaneous manifestations listed later in this paper in Table 3 were specifically noted for each patient. The presence of the systemic characteristics in Table 4 were prospectively recorded. The presenting symptom was also recorded for each patient and the laboratory values listed in Table 5 were determined for most of them.

Antibody to extractable nuclear antigen was determined by the hemagglutination method of Sharp and co-workers.[1] This test was carried out using ENA-coated sheep erythrocytes before and after ribonuclease (RNase) treatment. A fall in titer of four or more dilutions after treatment was interpreted as ribonuclease-sensitive and indicative of antibody to ribonucleoprotein.

Cutaneous immunoglobulin deposits were detected by direct immunofluorescence of biopsy specimens of both normal skin exposed to the sun (wrist and forearm) and nonexposed skin (medial forearm near the antecubital fossa, back or buttock) as previously described.[2]

The antinuclear antibody (ANA) test was carried out by the method of Holborow and colleagues[3]; total hemolytic complement (CH_{50}) by the method of Kabat and Mayer[4]; the third and fourth components of complement (C3 and C4) were measured by radial immunodiffusion; the $C1_q$ component of complement was determined by the method of Agnello and associates.[5] Antibody to double-stranded (native) DNA was determined by the millipore filter assay of Ginsberg and Keiser.[6] Ninety-five percent confidence intervals are recorded for each clinical or laboratory observation.

Results

Figure 1 shows anti-ENA titers before and after RNase digestion. Of the 46 patients designated as RNase sensitive, 45 had a fall in titer of a least four tube dilutions; 34 of these patients' titration values dropped to less than 1:200 after antigen digestion with RNase. Only three patients had appreciable titers of an RNase-resistant ENA (termed "anti-Sm"). Thirty-eight patients had anti-RNP

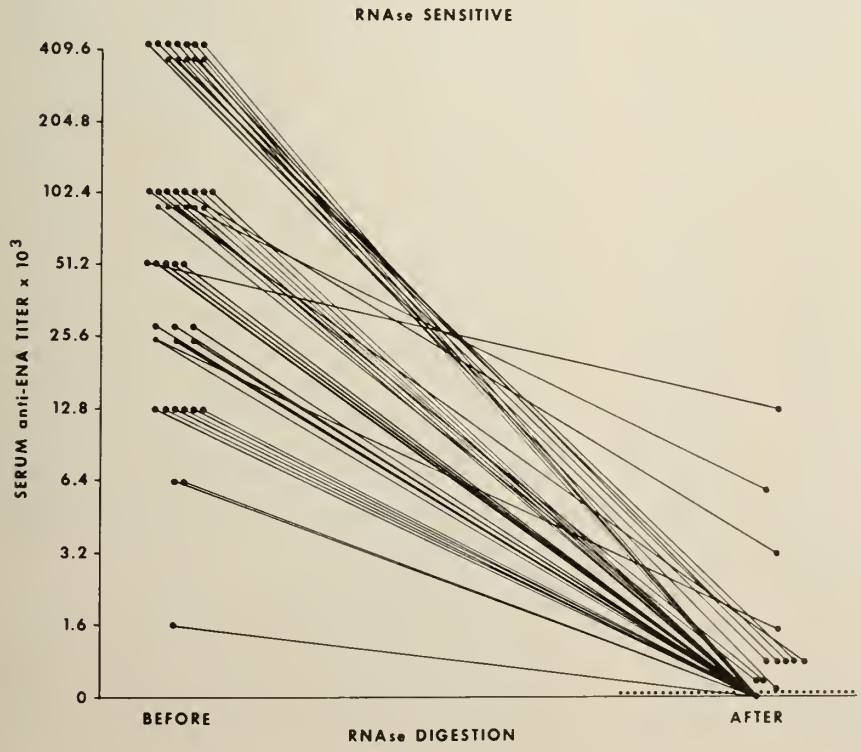

Figure 1.—Serum anti-ENA titers in 46 patients before and after ribonuclease digestion.

TABLE 1.—*Presenting Features in Patients With Mixed Connective Tissue Disease**

Presenting Feature	*Patients (%)*
Arthritis/arthralgia	21 (46)
Raynaud phenomenon	13 (28)
Cutaneous lupus erythematosus (LE)	7 (15)
chronic (discoid)	4 (9)
subacute	2 (4)
lupus profundus	1 (2)
Serositis	1 (2)
Nephrotic syndrome	1 (2)
Idiopathic thrombocytopenic purpura	1 (2)
Sclerodactyly	1 (2)
Alopecia	1 (2)

*All cases included presence of high-titer serum antibody to ribonucleoprotein.

TABLE 2.—*Development of Additional Signs or Symptoms in 46 Patients With Mixed Connective Tissue Disease*

	Years to Development of Next Manifestation			
	<1 Yr	*1-1.9 Yrs*	*2-3.9 Yrs*	*>4 Yrs*
Patients with arthritis	12	4	2	3
Patients with Raynaud phenomenon	6	1	2	4*
Patients with cutaneous lupus erythematosus	1	3	1	2

*Longest period to onset was 16 years.

TABLE 3.—*Cutaneous Manifestations in 46 Patients With High-Titer Antibody to Ribonucleoprotein*

	Patients	
Cutaneous Manifestation	*No. Positive (%)*	*Percentage with 95% Confidence Intervals*
Swollen hands or sclerodactyly	23 (50)	35-65
Cutaneous lupus erythematosus (LE)	22 (48)	33-63
chronic (discoid)	8 (13)	8-31
subacute	13 (28)	16-43
acute (malar)	4 (9)	2-21
lupus profundus	1 (2)	0-12
Periungual telangiectasia	21 (46)	31-61
Alopecia	21 (46)	31-61
Dyspigmentation	13 (28)	16-43
Photosensitivity	13 (28)	16-43
Vasculitis	10 (22)	11-36
Acrocyanosis	10 (22)	11-36
Mucous membrane ulceration	10 (22)	11-36
Pronounced facial telangiectasia	8 (17)	8-31
Erythema (elbows/knees/knuckles)	7 (15)	6-29
Cutaneous sclerosis	7 (15)	6-29
Livedo reticularis	7 (15)	6-29
Urticaria	5 (11)	4-24
Subcutaneous nodules	5 (11)	4-24
Heliotrope lids	3 (7)	1-18
Calcinosis cutis	2 (4)	1-15
Petechiae	2 (4)	1-15
Gottron papules	1 (2)	0-12

titers measuring 1:25,600 or greater. The mean titer was 1:149,200 and the median was 1:102,-400. The highest antibody titer was recorded for patients with several determinations; sera were not diluted greater than 1:409,600.

The presenting clinical features are shown in Table 1. Additional clinical signs or symptoms developed in most of the patients within two years (Table 2). The Raynaud phenomenon usually developed early in the course of the disease when it was not the presenting feature. In 15 patients it occurred in less than a year; in four it developed in less than two years, and in five it occurred in less than four years. In six others it occurred more than four years after onset of MCTD (the longest period was 12 years). The three patients in whom the Raynaud phenomenon had not yet developed, had had MCTD for two, four and six years, respectively, at the time of the study.

Table 3 shows the cutaneous manifestations of the 46 patients. Swollen hands or sclerodactyly were observed in 23 patients (50 percent). Most of these patients had puffy fingers, without much cutaneous sclerosis; only two patients had tightly bound-down skin with contractures. The entire spectrum of cutaneous LE was observed: 8 patients had persistent destructive discoid lesions, 13 had diffuse, nonscarring, poorly demarcated subacute lesions and 4 patients had an acute malar eruption. Pigmentary disturbances were found in 13 patients (28 percent), and included focal and diffuse hyperpigmentation, poikiloderma, vitiligo and hypopigmentation with follicular retention of pigment (the "salt and pepper" depigmentation of scleroderma). Cutaneous vasculitis was present in ten patients (22 percent). This group included patients with biopsy-proved leukocytoclastic vasculitis manifested clinically by purpuric papules and ulcers on the legs as well as patients with transient, painful dermal nodules that often occurred on the hands. These nodules usually lasted two to six weeks and resolved without scarring. Biopsy specimens showed either a perivascular lymphocytic infiltrate or leukocytoclastic vasculitis. Other cutaneous findings are listed in the table.

Table 4 depicts the systemic clinical features of the 46 patients. Raynaud phenomenon occurred in 43 (93 percent) and was frequently the most persistent and bothersome symptom as well as the one least responsive to therapy. The arthritis was usually evanescent and nondeform-

ing as usually occurs in SLE. Only four patients had a deforming arthritis; two of these had mild to moderate erosive changes noted on x-ray films. Mild myalgia, fatigue and weakness were observed in 26 patients (57 percent); moderate to severe myositis with elevated muscle enzymes was less frequent (26 percent). Five patients had lymph node biopsies done to rule out a lymphoproliferative malignant condition. Episodes of pleurisy (14 patients) or pericarditis (seven patients) occurred in 35 percent. Prolonged hoarseness (unassociated with sicca syndrome) was observed in 28 percent. Renal disease was present in eight patients, manifested as persistent mild proteinuria (two), mesangial or focal glomerulitis (two), membranoproliferative glomerulonephritis (one) and membranous glomerulonephritis (three). At present, only one of these patients has renal insufficiency. Four patients had central nervous system disease, three had trigeminal sensory neuropathy and one had a bilateral neurosensory hearing loss. No patients had seizures, psychoses or strokes. Other features are listed in the table.

Table 5 summarizes the laboratory findings in these patients. In all patients results of ANA tests were positive, 83 percent with high titers. The immunofluorescent nuclear staining patterns were as follows: speckled, 39 (85 percent); speckled only, 28 (61 percent); homogeneous, 18 (39 percent), and peripheral, 9 (20 percent). The nucleolar staining pattern was not observed. Seventeen (37 percent) of the patients had two or more patterns.

Speckled (particulate) epidermal nuclear IgG deposition occurred in 91 percent on direct immunofluorescence of normal skin. This immunofluorescent marker for very high-titered ENA antibody has been described in detail elsewhere.[7-10] The 91 percent prevalence of epidermal nuclear IgG localization in MCTD is probably too high since many of these patients were selected for another study by this finding.[9,10]

Esophageal dysmotility occurred in 61 percent of the patients although dysphagia was present in only 15 percent. Abnormal pulmonary function tests were present in 59 percent of those tested. Some 38 percent had a mild restrictive defect, 34 percent had a mild diffusion defect and 13 percent had abnormal restrictive and diffusion tests. Generally, x-rays of the chest showed no abnormalities in these patients.

Subepidermal immunoglobulins in normal skin (positive lupus band test) were observed in 15 of 44 (34 percent) patients. In 13 of 34 (38 percent) patients, tests were positive on sun-exposed skin; 6 of 28 (21 percent) were positive on skin not exposed to the sun. The frequency distribution of subepidermal immunoglobulin deposits in these 15 patients included IgG and IgM in five, IgG only in six and IgM only in

TABLE 4.—*Systemic Characteristics of 46 Patients With High-Titer Antibody to Ribonucleoprotein*

Systemic Characteristic	*Patients* No. Positive (%)	*Percentage With 95% Confidence Intervals*
Raynaud phenomenon	43 (93)	82-99
Arthritis or arthralgia	42 (91)	79-98
Adenopathy	20 (43)	29-59
Vascular headache	16 (35)	21-50
Pleurisy/pericarditis	16 (35)	21-50
Prolonged hoarseness	13 (28)	16-43
Hepatomegaly/splenomegaly	13 (28)	16-43
Myositis	12 (26)	14-41
Sicca syndrome	11 (24)	13-39
Renal disease	8 (17)	8-31
Dysphagia	7 (15)	6-29
Central nervous system disease	4 (9)	2-21
Dyspnea	4 (9)	2-21
Thrombophlebitis	2 (4)	1-15
Thyroid disease	2 (4)	1-15
Idiopathic thrombocytopenic purpura	2 (4)	1-15

TABLE 5.—*Laboratory Findings in 46 Patients With High-Titer Antibody to Ribonucleoprotein*

Studies	*Patients* No. Studied	No. Positive (%)	*Percentage With 95% Confidence Intervals*
"Anti-RNP" antibody	46	46 (100)	
Antinuclear antibody	46	46 (100)	92-100
Epidermal nuclear IgG deposition	44	40 (91)	78- 97
Hypergammaglobulinemia	40	31 (78)	62- 89
Erythrocyte sedimentation rate (>30 mm per hour)	43	33 (77)	61- 88
Esophageal dysmotility	33	20 (61)	42- 77
Abnormal pulmonary function	32	19 (59)	41- 76
Rheumatoid factor	46	26 (57)	41- 71
LE cells	41	15 (37)	22- 53
Lupus band test	44	15 (34)	20- 50
Hypocomplementemia	43	12 (28)	15- 44
Elevated anti-nDNA	43	9 (21)	10- 36
Leukopenia (leukocytes <4,000 per cu mm)	44	9 (20)	10- 35
Direct Coombs test	27	5 (19)	6- 38
Anemia (Hb <11 grams per dl)	44	8 (18)	8- 33
Cryoglobulinemia	30	4 (13)	4- 31
Biologic false-positive ([+] VDRL; [−] FTA-ABS)	36	2 (6)	1- 19

four. In 16 patients biopsy specimens were taken simultaneously from both sites: both tests were positive in three patients and both tests were negative in ten patients; in three patients (19 percent) tests were positive on sun-exposed sites and negative on nonexposed skin.

Twelve patients (28 percent) had hypocomplementemia. In 11 of these there was only mild to moderate depression of serum complement. In one patient hemolytic complement was substantially depressed for a prolonged period. Her anti-nDNA was within normal limits, however, and she had no clinical evidence of renal disease. Some 21 percent of the patients had elevated serum antibodies to nDNA. Mild to moderate titers were present in seven patients; two patients had high titer antibodies to nDNA. Of the latter, one patient had no clinical evidence of renal disease and the other had membranous glomerulonephritis without renal insufficiency. Other laboratory abnormalities are noted in Table 5.

Discussion

Frequently, there appears to be little value in discussing whether a patient suffers from a specific disease, and the diagnosis becomes almost a matter of opinion.[11] Sharp and co-workers[1,12] have contributed to medicine by carefully defining a characteristic subset of connective tissue disease (CTD). Many, if not most, of these patients may fulfill arbitrary criteria for other diagnoses of CTD. However, it appears that most patients seen at university hospitals with high-titer antibody to RNP (without appreciable amounts of "anti-Sm") have clinical or laboratory manifestations of two or more CTD.

The purpose of this report is to extend the RNP spectrum of CTD to include a patient population more representative of private practice. Approximately 75 percent of the patients in this report are managed by physicians in private practice or in the military. In general, these patients as a group, have a milder form of the RNP subset than previously reported.[1,8,12-15]

The diagnosis of RNP subset or MCTD should be suspected in patients with Raynaud phenomenon and nondeforming (nonerosive) arthritis or arthralgia. Such cases are sometimes misdiagnosed as rheumatoid arthritis because these patients frequently have high-titered rheumatoid factors (RF). It appears that moderate to severe erosive arthritis is uncommon in patients with anti-RNP even in the presence of prolonged elevations of RF. The combination of subacute or chronic cutaneous lupus erythematosus, Raynaud phenomenon and arthralgia is frequently observed by dermatologists and appears to have a high association with anti-RNP. We recently observed the high prevalence of subacute and chronic cutaneous LE in this RNP subset.[8] We also reported two patients with discoid lupus erythematosus (DLE) in whom MCTD (RNP subset) developed.[16] Six additional such patients are reported here.

The association of frequent mild to moderate vascular headaches with anti-RNP has been noted recently. Most of these patients with cyclical, throbbing headaches experienced prodromal symptoms (eight had visual auras), and five suffered nausea or vomiting. None of the 16 patients with vascular headaches had prominent suboccipital pain or tension suggestive of the diagnosis of muscle contraction headaches. The high prevalence of vascular headaches may be related to the Raynaud phenomenon. A detailed neurologic investigation of vascular headaches in MCTD has been reported elsewhere.[17]

Frequent episodes of prolonged hoarseness, lasting for weeks, appear to be a new finding. However, none of the 13 patients in whom hoarseness occurred had sicca syndrome. Many of them had frequent ear, nose and throat examinations which gave normal findings. Myositis (myalgia and objective muscle weakness with increased muscle enzyme values) was much less common in this series than in previous reports.[1,12-15] Muscle weakness was frequently clinically more prevalent than the objective laboratory tests indicated (muscle enzymes, electromyogram and muscle biopsy).

Sicca syndrome (xerostomia or keratoconjunctivitis sicca) occurred in 11 patients. In eight of these patients there was either an abnormal finding on a Shirmer test or a lip biopsy gave positive findings, indicating focal lymphocytic infiltration into affected glandular tissue.[18]

The low prevalence of severe central nervous system disease and progressive renal insufficiency is perhaps the most important feature of the RNP subset and has been previously well described.[1,8,12-14,19,20] Of note is the high prevalence of abnormal pulmonary function test results (59 percent) and esophageal dysmotility (61 percent) associated with a low prevalence of dyspnea (9 percent) and dysphagea (15 percent).

The cutaneous manifestations of the 46 patients primarily show features of SLE and sclero-

derma. A low prevalence of typical skin changes suggestive of dermatomyositis was noted. The most striking skin lesions were cutaneous LE (48 percent) and swollen hands or sclerodactyly (50 percent). However, extensive cutaneous sclerosis that characterizes scleroderma was uncommon (15 percent). Alopecia, though common (46 percent), was usually mild. Often a beautician or spouse first noted the loss of hair. The clinical appearance of hair loss was that of a prolonged telogen effluvium. In most cases, the patient's hair appeared normal and only a careful history showed that significant hair loss had occurred. These cutaneous findings are similar to those we have previously reported.[8]

It is likely that all patients had high-titer speckled (particulate) antinuclear antibodies at some time during their course because anti-ENA is associated with a speckled pattern, and the pattern observed by direct immunofluorescence of normal skin was also speckled. The homogeneous pattern may have obscured the speckled pattern in certain patients when both were present in high titer.

Most of the patients had relatively mild disease and usually responded rapidly to low-dose corticosteroid therapy. Patients with arthralgia, myalgia and fatigue often responded well to nonsteroid anti-inflammatory agents alone. However, Raynaud phenomenon was resistant to all forms of therapy.

Antibody to RNP appears to be another in a growing list of immunologic markers associated with certain distinct clinical manifestations. The early differentiation of this RNP subset—involving a less aggressive clinical course characterized by a high prevalence of the Raynaud phenomeon, a low prevalence of progressive renal insufficiency and severe CNS disease and a good response to low-dose corticosteroids—is important for prognostic purposes.

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Clinical Value of Teichoic Acid Antibody Titers in the Diagnosis and Management of the Staphylococcemias

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Differentiation of endocarditic from nonendocarditic Staphylococcus aureus *(SA) septicemia is prognostically and therapeutically important. A study of 68 cases of either SA or streptococcal sepsis, including 50 cases of SA sepsis of both cardiac and noncardiac origin, was done to determine the presence and titer of serum teichoic acid antibodies (TAA's) by double immunodiffusion. Thirty-seven uninfected controls were also examined. There was no statistical difference in either incidence or peak TAA titers in endocardial versus deep-seated, extracardiac SA sepsis. However, in both of these groups, incidence and peak titers were significantly higher than in intravascular catheter-related SA sepsis, streptococcal endocarditis and controls ($P<0.05$). Peak TAA titers in SA sepsis develop on admission or shortly thereafter (6 to 11 days) and permit early decisions on degree of tissue infection, likelihood of metastatic seeding and necessity for higher-dose, longer-term antibiotic therapy.*

Cases of catheter-related SA sepsis with no clinical evidence of metastatic SA seeding and with negative or low-titered (1:1) TAA's were classified as superficial sepsis. Treatment consisted of short-term, low-dose antistaphylococcal regimens and catheter removal. In posttherapy follow-up after 6 to 12 weeks, all of the patients were cured and no signs of endocarditis or deep-seated SA infection developed.

Staphylococcus aureus (SA) is a major cause of bacterial endocarditis as well as septicemias arising from noncardiac sources.[1,2] To distinguish endocardial from nonendocardial *S aureus* bacteremias can be very difficult, and, frequently, the determination is based on clinical or relatively nonspecific laboratory measurements. However, this diagnostic differentiation is of utmost prognostic and therapeutic importance.[2,3] Several previous studies of relatively small numbers of patients have suggested determining teichoic acid antibody (TAA) titers by gel diffusion to assist in

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ABBREVIATIONS USED IN TEXT

CIE = counterimmunoelectrophoresis
DID = double immunodiffusion
IE = infective endocarditis
SA = *Staphylococcus aureus*
TA = teichoic acid
TAA = teichoic acid antibody

the serodifferentiation of cardiac from noncardiac SA sepsis.[4,5] We report our prospective experience with 50 consecutive patients with SA bacteremias and emphasize the usefulness of this test in the diagnosis and management of the various staphylococcemic syndromes.

Patients and Methods

In a prospective study including 105 patients, agar gel double immunodiffusion (DID) and counterimmunoelectrophoresis (CIE) techniques were used to determine the presence or titer, or both, of precipitating serum antibodies against the α-ribitol and β-ribitol teichoic acids (TA) found in the cell wall sonicate of coagulase-positive SA.[4,5] Teichoic acid antibodies (TAA's) were assayed in four distinct groups of subjects, roughly similar in age and sex distribution (Table 1).

Staphylococcus aureus *Infective Endocarditis*

One group was made up of 22 patients who fulfilled strict criteria for the diagnosis of SA infective endocarditis.[6,7] Clinically, patients had to have compatible medical histories (such as rheumatic or atherosclerotic valve disease or intravenous drug addiction), appropriate symptoms (especially fever, back pain and arthralgias[8]) and certain physical findings suggestive of infective endocarditis (IE), such as pleuritis (as a manifestation of right-sided IE), splenomegaly or cardiac valvulitis (particularly newly developing regurgitant murmurs[3]). In addition, presence of hematuria, hypocomplementemic renal insufficiency, positive serum VDRL and rheumatoid factor assays were frequently useful in support of the diagnosis. Bacteriologic confirmation was made by isolating *S aureus* organisms from multiple blood cultures (three or more sets, each including one anaerobic and one aerobic bottle) on one day or from serial blood cultures over two or more days.[6,7] Further supportive data, such as chest x-ray findings (for evidence of septic emboli from the right side of the heart), echocardiograms (to screen for valvular vegetations or underlying valvular abnormalities[3]) and, at times, cardiac angiograms, surgical or autopsy findings were used. Patients with SA sepsis from an unidentifiable primary focus, though often treated for SA IE,[1] were not included. Also, no patients who were concurrently receiving steroid or cytotoxic therapy, which might influence TAA titers, were included.

TABLE 1.—*Clinical Groups Assessed for Presence and Titer of Serum Antiteichoic Acid Antibodies by Agar Gel Double Immunodiffusion*

Patient Group	*Number (Total = 105)*
Staphylococcus aureus endocarditis	22
Nonendocarditic *S aureus* septicemia	28
Superficial	
Infected intravascular catheter	9
Cellulitis	1
Deep-seated	
Pneumonitis	5
Intra-abdominal abscess	5
Osteomyelitis	3
Septic arthritis	3
Cerebral abscess	1
Epidural abscess	1
Streptococcal endocarditis	18
Uninfected controls	37

Non-IE SA Sepsis

A second group included 28 patients with SA bacteremia arising from clearly definable noncardiac sites. The group was further subdvided (Table 1) by whether staphylococcemia arose from superficial foci (such as cellulitis or infected intravascular catheters) or from deep-seated SA infection (such as osteomyelitis). Patients clinically judged to have superficial SA sepsis were serially investigated for evidence of occult metastatic seeding by: (1) ophthalmoscopy to screen for hematogenous endophthalmitis, (2) urine cultures, intravenous pyelography or abdominal ultrasonography, or both, to rule out hematogenous perinephric or intrarenal abscess,[9] and (3) gallium citrate Ga 67 body scanning to screen for an inapparent, metastatic SA focus.

Non-SA Gram-Positive Coccal IE

Eighteen patients were in this category. Similar strict criteria, as above, were used in the diagnosis of infective endocarditis. Of the cases 11 were due to *S viridans;* the remaining seven were caused by enterococcal organisms.

Controls

This group included 13 patients who were active intravenous users of heroin but had no evidence of bacterial infections. None of the 13

Figure 1.—Example of agar gel diffusion for determining teichoic acid precipitin (Ppt) titers. Teichoic acid antigen (T.A.Ag.) is in the center well, with serial dilutions of serum (1:1 to 1:16) and γ-globulin in the outer wells. In this example, the titer is 1:4.

were nasopharyngeal SA carriers at the time sera were obtained. Also studied were 24 healthy laboratory personnel with no history of illicit drug use or active infection.

Antigen Preparation

A cell wall sonicate of SA (Laffery strain, phage type 52/42B/80/81 [provided by Drs. Arthur White and Joseph Wheat], containing both α- and β-N-acetyl-glucosaminyl-ribitol teichoic acids[4]), was prepared by previously described methods.[10] TA antigen contained in the sonicate was removed after centrifugation, standardized using specific anti-TAA raised in rabbits, and stored at −5°C until tested. The TA sonicate antigen developed lines of identity with purified TA by DID.

Double Immunodiffusion in Agar

Agarose (1 percent) in barbital buffer (pH 8.6, M = 0.025) was used for double immunodiffusion (DID) testing for TAA's. Briefly, seven circular wells, one central and six peripheral, were cut in agarose gel with a metal template. The holes were 3 mm in diameter and 7 mm apart (Figure 1). The TA antigen (1:1, 1:2 and 1:4 dilutions) was placed in the central well, with serial twofold saline dilutions of serum placed in outer wells (numbers 1,3,4,5,6). Outer well number 2 was filled with immune serum γ-globulin (Gammagee, 165 mg per ml, Merck, Sharpe and Dohme) to delineate reference lines of identity with TA-TAA precipitin bands.[10] If the TAA titer by DID was 1:16, a second assay was run, with serum diluted 1:32 to 1:512.

Counterimmunoelectrophoresis in Agar

Counterimmunoelectrophoresis (CIE) plates were prepared with 1 percent agarose in barbital buffer (pH 8.6, M = 0.075). The template pattern cut in the gel, TA sonicate and serum dilutions, and CIE technique followed previously described methods.[5] A serum containing high-titered TAA served as a positive control. Slides were read as positive or negative for precipitin bands and not titered because of difficulty in reproducing exact titers by this technique;[5,12] the CIE test thus served as a screening procedure for presence of TAA's.

Serum Specimens for Teichoic Acid Antibodies

In patients with infective endocarditis, at least two serum specimens, taken a week apart, were tested for TAA's. The initial specimens were generally obtained within 72 hours after patients were admitted to hospital, and further specimens drawn at weekly intervals, as possible, until discharge and during posttherapy follow-up. The peak DID titer was used for statistical comparisons.

In cases of non-IE SA sepsis, two serum specimens, taken a week apart, were usually obtained. In patients who were in hospital for longer periods, further weekly specimens were drawn. As above, the peak DID titers were used in comparative assessments.

To be included in this study, all staphylococcemic patients had to have serum samplings to at least 14 days after onset of illness.[5,12]

No patients in either staphylococcemic group received antibiotics before admittance to hospital.

Of the 37 noninfected controls, only one serum sample was obtained for serologic testing.

Therapy and Follow-up of Staphylococcemic Patients

Patients with SA infective endocarditis were treated for four to six weeks with high-dose parenteral antistaphylococcal agents.[13] Patients with non-IE, deep-seated SA sepsis were placed on antibiotic regimens according to site of infection, but generally received parenteral therapy for a minimum of three weeks, combined with appropriate drainage procedures and extended courses

of antibiotics given orally where indicated (such as *S aureus* osteomyelitis).

In contrast, patients with superficial SA sepsis with no evidence of metastatic seeding and negative or low (1:1) DID-TAA titers on serial assays were treated with short-term (seven to ten days), low-dose parenteral antistaphylococcal regimens with drainage or catheter removal as indicated.

The conditions of all patients with non-IE SA sepsis were followed clinically for a minimum of six weeks after therapy (range, 6 to 12 weeks) for any evidence of the development of IE.

Statistical Analyses

Incidences of positive TAA determinations in the four study groups were compared by chi square (x^2) analysis. DID titers were contrasted by Student's *t* test.

Results

SA IE

Of these 22 patients, 21 (95 percent) had positive DID-TAA titers ($\geq$1:1); the remaining patient, negative by DID, had a positive CIE screen. Eleven of the 21 (55 percent) positive DID reactors had peak TAA titers of at least 1:4; the highest peak DID titer obtained was 1:16.

Examination of the serial evolution of DID-TAA titers in this group showed that in 15 of 21 cases with positive tests (71 percent), maximum titers were present on admission into study. The remaining six patients had rising titers after entry into the study, with peaks noted at a mean of 6.6 days (range, 3 to 10 days).

Nine of these patients had long-term serologic follow-up into convalescence (2 to 12 weeks after therapy). Of note, in seven of the nine (78 percent), TAA titers fell to zero or low, stable titers (usually 1:2 or lower) with successful treatment. In the two remaining patients, each with low peak titers (1:1 and 1:2, respectively), there was no titer decline in convalescence, despite clinical and bacteriologic cure.

Non-IE SA Sepsis

In 16 of the 18 patients (88 percent) with deep-seated SA infection TAA titers were detectable by DID; the remaining two patients had positive CIE screening assays.

In contrast, just three of ten patients (30 percent), with SA sepsis from superficial infectious foci, had positive DID tests ($P<0.025$, x^2 analysis). In an additional three patients there were positive findings on CIE screens, while results remained negative on serial DID testing; in the other four patients findings were negative on both CIE and DID testing.

Seven of the 18 patients (39 percent) with deep-seated SA infections versus none of the ten patients with superficial SA sepsis had peak DID-TAA titers of at least 1:4 ($P<0.05$, x^2 analysis). Of note, the proportion of patients with deep-seated SA sepsis and DID titers of 1:4 or higher, was not statistically different from the SA IE group (Table 2, Figure 2).

Among patients with deep-seated SA sepsis, the highest peak DID-TAA titer observed was 1:32, while the three patients with SA sepsis from superficial infection and positive DID assays each had low peak titers of 1:1.

Serial DID-TAA titering showed that in eight of

TABLE 2.—*Results of DID and CIE Tests for Detection of Antiteichoic Acid Antibodies*

Patient Group (Total=105 patients)	*Number (Total =105)*	*Percent Positive*		*Percent with DID titer >1:4*
		DID	*CIE*	
Staphylococcus aureus endocarditis	22	95*	100	55†
Nonendocarditic *S aureus* septicemia	28	70	90	25
Deep-seated	18	88*	100	39†
Superficial	10	30	60	0
Streptococcal endocarditis	18	17	33	0
Uninfected controls	37	5	22	0

CIE=counterimmunoelectrophoresis; DID=double immunodiffusion

*P=<0.0005, x^2 analysis
†P=<0.05, x^2 analysis

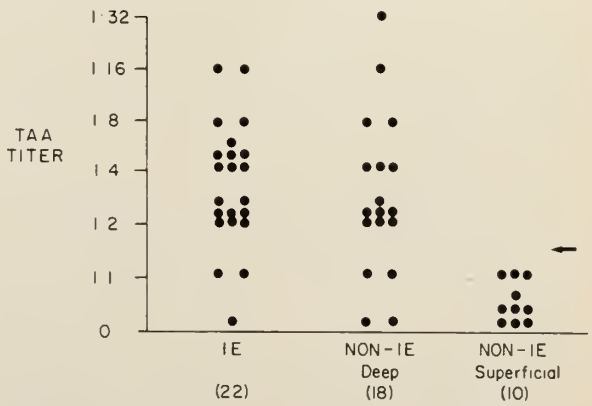

Figure 2.—Distribution of peak teichoic acid antibody-double immunodiffusion (TAA-DID) titers in various staphylococcemic groups. Arrow indicates distribution break-point of TAA-DID titers, separating the deeper, from more superficial staphylococcemic syndromes.

16 (50 percent) patients with positive reactions and deep-seated SA infection, peak titers were present on initial sampling. In the other eight patients in this group, maximum DID titers developed at a mean of 11.4 days (range, 7 to 16 days) after entry into the study. Of the three patients with superficially arising SA sepsis and positive DID tests, one had a peak titer (1:1) on admission, while in the other two patients peak titers (1:1 in each) developed at five and seven days following admission, respectively.

The cases of seven patients with deep-seated SA sepsis were followed serologically for at least two weeks after cure of infection; in five cases, serial DID titers fell gradually to zero or low, stable titers (1:1 or 1:2, Figure 3). In the other two patients, as well as in the three patients with superficial sepsis and positive DID tests, TAA titers persisted at low levels (1:1) despite microbiologic and clinical cures.

Non-SA, Gram-Positive Coccal IE

Among the 18 cases in this group, there were three (17 percent) with detectable, low TAA titers

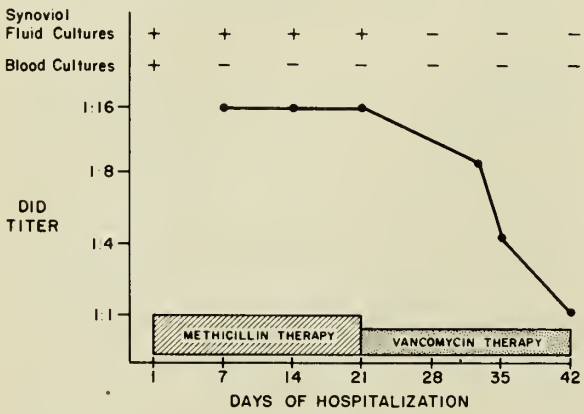

Figure 3.—Serial teichoic acid antibody titers by agar gel double immunodiffusion (DID) in a patient with *Staphylococcus aureus* septic arthritis, osteomyelitis and bacteremia.

TABLE 3.—*Mean Peak Teichoic Acid Antibody Titers by Agar Gel Double Immunodiffusion in 68 Patients With Gram-Positive Coccal Septicemia*

Patient Group	*Number*	*Mean Peak Titer ±SEM*†
Staphylococcus aureus endocarditis	22	4.27±0.89*
Nonendocarditic *S aureus* septicemia	28	3.37±1.21*
Deep-seated	18	4.84±1.69*
Superficial	10	0.33±0.15
Streptococcal endocarditis	18	0.15±0.07

*P<0.05, Student's *t* test.
†For statistical comparisons, reciprocals of the highest TAA titers were used.

by DID (all three, 1:1). In an additional four patients, in whom findings were negative by DID, results were positive by CIE (22 percent). These cross-reactivity rates are not dissimilar to those noted by Tuazon and co-workers.[5,12] In serial DID testing, the three with positive titers (1:1) remained serofast throughout the therapy and convalescent phases (5 to 12 weeks).

Controls

None of the 13 uninfected drug addicts and two of the 24 healthy controls (5 percent) had TAA titers detectable by DID (1:1, in each). An additional eight patients (22 percent) with negative DID tests had positive CIE screens.

Statistical Comparisons—SA IE Versus Noncardiac SA Sepsis

When mean peak TAA-DID titers were compared in the SA IE group versus the deep-seated SA sepsis cases, there were no statistical differences noted (Table 3). In contrast, in both of these latter groups, mean peak titers were significantly higher than in the group of patients with superficial SA sepsis ($P \leq 0.025$ and $P \leq 0.005$ for deep-seated and IE-related staphylococcemias, respectively, Student's *t* test).

SA IE and Deep-Seated Non-IE SA Sepsis Versus Streptococcal IE and Controls

In the patients with deep-seated SA sepsis and SA IE, mean peak DID titers were significantly higher than those seen with either streptococcal IE or among uninfected controls ($P < 0.05$, Student's *t* test).

Clinical Follow-up of Staphylococcemic Patients

As noted above, in patients clinically-assessed to have SA sepsis from superficial infections and in whom no evidence of metastatic SA seeding occurred (ten patients), we utilized the peak TAA-DID titer to guide our therapy. No patients had DID titers above 1:1 and all received short-term, low-dose antimicrobial treatment with appropriate drainage or foreign-body removal. Of note, in no patients judged to have superficial SA sepsis by the clinical-serologic criteria, did either SA IE or evidence of metastatic seeding develop during the 6 to 12 weeks of follow-up.

Discussion

When faced with SA sepsis, the differentiation of a valvular versus a noncardiac source is of

utmost therapeutic and prognostic importance. In patients with SA IE, especially involving the aortic or mitral valves, prolonged antimicrobial therapy is required,[14] destructive valvulitis frequently develops necessitating prosthetic valve replacement[2] or there are septic emboli to distant foci.[15] These factors are reflected in the nearly 50 percent mortality cited for patients with this disorder[3,14] despite the advent of newer and more powerful antistaphylococcal agents. In contrast, patients with SA sepsis arising from focal suppuration or removable sources of infection tend to be more readily cured with shorter-term antibiotic therapy and appropriate drainage procedures, with much lower mortality.[16] Thus, distinguishing between these two staphylococcemic syndromes has been the subject of intensive investigation.

In patients with SA sepsis and no clinical evidence of IE, many physicians have elected to empirically treat patients as if IE were present.[2] This approach is based on controversial data from Wilson and co-workers,[17] that over 50 percent of patients with SA sepsis will have underlying IE. Their study population, however, was biased with a large percent of patients having antecedent rheumatic or congenital heart disease. Nolan and Beaty[1] have also proposed that differentiation of cardiac from noncardiac SA sepsis could be made clinically. Their recent retrospective analysis disclosed that SA sepsis with no identifiable primary source and complicated by metastatic staphylococcal abscesses was statistically more likely to represent IE. Their findings, however, are in contrast to those of Bowmer and Robson[18] who, in an autopsy-confirmed series, could not clinically distinguish these two bacteremic syndromes by the identification of metastatic infectious foci. These conflicting clinical data and the potentially serious side effects (especially renal toxicity and ototoxicity[19,20]) associated with long-term, high-dose antistaphylococcal regimens used to treat SA IE have made it mandatory that more objective, and specific laboratory procedures be developed to differentiate IE from non-IE SA sepsis.

Studies of pathogenic strains of *S aureus* from serious human infections have shown that more than 96 percent contain either α-ribitol or β-ribitol teichoic acids.[12] Recently, through the investigations of White and colleagues[10] and Tuazon and associates,[4,5] the detection and determination of TAA titers in sera of patients with SA sepsis have been advocated as a relatively simple and specific method to distinguish between cardiac and noncardiac foci. Tuazon and co-workers were able to define a DID-TAA titer of 1:4 as a diagnostic *cut-off*. Patients with non-IE SA sepsis in their studies rarely had titers above 1:4 (none of six in one study), while 18 of 28 cases of SA IE had TAA titers of at least 1:4. In addition, the cross-over reaction rate, though 22 percent with streptococcal IE, was generally of low magnitude (titers, 1:1). Moreover, patients with no active infections had a low incidence (6 percent) of false-positive TAA reactions by DID, and when present, were also usually of low titer (1:1).

Because of the therapeutic and prognostic importance of the above observations and the relative ease in doing the DID assay, we sought to prospectively investigate the clinical use of the test in a large group of staphylococcemic patients. Our data would indicate that serum TAA titers in patients with SA sepsis have limited usefulness in distinguishing a cardiac from a noncardiac source. In our study in only 55 percent of patients with positive DID assays and documented SA IE did TAA titers of 1:4 or greater develop, despite multiple sera samplings both before and during antibiotic therapy. Similarly, in 44 percent of patients with deep-seated, noncardiac SA sepsis and positive DID reactions, TAA titers of 1:4 or greater developed. In addition, the mean TAA titer was not statistically different in patients with cardiac or noncardiac SA sepsis.

Critically assessing the value of TAA-DID testing in previous reports[4,5,15,21,22] and in our own study has led to the following statistical conclusions: (1) In general, titering of TAA's is of limited value in distinguishing SA IE from other deep-seated SA septicemias. (2) In patients with noncardiac SA septicemia, the presence of a positive DID titer, especially a titer of 1:2 or greater, is indicative of deep-seated infection and probable metastatic seeding,[15] and longer-term (two to four weeks) antistaphylococcal therapy appears justified. (3) Alternatively, noncardiac SA sepsis, particularly catheter-related and associated with negative or low DID-TAA titers (1:1), will statistically have no metastatic seeding and can be managed by catheter removal, and short-term antibiotic therapy.[15,16] (4) In patients with SA sepsis, peak DID-TAA titers are likely to occur relatively early, either on admission or within two weeks of admission to hospital, and allow the clinician to make a rational diagnostic assessment and determine need for more prolonged, higher-dose antistaphylococcal therapy. (5) Serial quantitation of

DID-TAA titers, in patients with either SA IE or noncardiac, deep-seated SA sepsis, will generally show there to be a sequential decline in titers paralleling the clinical and microbiologic efficacy of therapeutic regimens and, thus, could be employed to follow the course of such infections. (6) Because positive DID-TAA titers developed in 88 percent to 95 percent of patients with deeper-seated SA bacteremic syndromes, this assay may be potentially useful in identifying suspected serious SA infections, particularly IE, in patients with negative blood cultures (following preadmission antimicrobial therapy, for example). The only difficulty, in this regard, is the occasional false-positive, cross-reactivity of the DID-TAA assay, at low serum titers (1:1), in patients with other Gram-positive infections, particularly streptococcal IE (range, 17 percent to 22 percent[5,12]).

It is important to emphasize that we have used the DID-TAA assay to guide our antistaphylococcal regimens in a limited number of patients (ten) with presumed intravascular catheter-related SA sepsis. In all ten patients there were negative or low-titered (1:1) DID-TAA assays, and each patient received short-term, low-dose antistaphylococcal therapy, combined with catheter removal. Of note, in no patient did evidence develop of SA IE or deep-seated, metastatic SA infection over a 6 to 12 week follow-up. We are now using these serologic approaches in larger groups of staphylococcemic patients in the hope of confirming these preliminary findings.

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Multiple Endocrine Neoplasia Syndromes

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The multiple endocrine neoplasia (MEN) syndromes consist of three distinct disease entities. They have in common adenomatous, carcinomatous or hyperplastic involvement of a variety of endocrine glands, and an autosomal dominant inheritance. MEN I includes hyperparathyroidism, islet cell and pituitary tumors. The components of MEN IIa are hyperparathyroidism, medullary thyroid carcinoma and pheochromocytoma. MEN IIb includes multiple neuromas, medullary thyroid carcinoma and pheochromocytoma. Effective tests are available for the early detection of components of the syndromes in potentially affected patients. Screening can lead to therapeutic intervention before clinical sequelae ensue.

THE PRESENCE of more than one endocrine tumor in an individual person can occur by chance alone. However, the development of endocrine gland tumors in a defined anatomic and familial pattern constitutes the multiple endocrine neoplasia (MEN) syndrome. In 1903 Erdheim[1] described the case of a patient with acromegaly and four enlarged parathyroid glands. Cushing and Davidoff[2] noted a patient with acromegaly, two parathyroid adenomas and an islet cell tumor. Rossier[3] was first to describe a family with numerous members affected by endocrine gland tumors. Wermer[4] in 1954 collected data involving several families and suggested that the disease was transmitted by a single autosomal dominant gene. Ballard and co-workers[5] wrote a landmark paper on the subject in 1964. They traced six generations of a family affected by multiple endocrine syndrome, type I, and reviewed the world's literature on the subject. They carefully defined the main components as involvement of the pituitary, pancreas and parathyroid glands.

In 1959 Hazard and Crile[6] recognized and named medullary thyroid carcinoma. The chief features differentiating this malignant condition from anaplastic thyroid carcinoma were the regular appearance of amyloid in the stroma and a relatively benign course. In 1961 Sipple[7] noted the increased frequency of thyroid tumors in patients with pheochromocytoma. However, he probably did not recognize that all of these thyroid tumors were of the medullary type. In 1966 Williams collected 67 cases of medullary thyroid carcinoma.[8] He noted the familial association and concurrent presence of pheochromocytoma in some patients. Steiner and co-workers[9] in 1968 traced seven generations of a family with members having medullary thyroid carcinoma, pheo-

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
APUD = amine precursor uptake and decarboxylation
MEN = multiple endocrine neoplasia
MCT = medullary carcinoma of the thyroid
PTH = parathyroid hormone
ZES = Zollinger-Ellison syndrome

chromocytoma or hyperparathyroidism, or combinations of these conditions. Because no member of this kindred had either islet cell or pituitary involvement, they felt that the association of pheochromocytoma, medullary thyroid carcinoma and hyperparathyroidism constituted a distinct genetic syndrome. They named it multiple endocrine neoplasia, type II.[9]

In 1968 Gorlin and co-workers noted some patients with medullary thyroid carcinoma, pheochromocytoma and multiple mucosal neuromas with or without a marfanoid habitus.[10] Subsequently, several groups have advocated that the association of mucosal neuromas, pheochromocytomas and medullary thyroid carcinoma be called multiple endocrine neoplasia, type III[11] or type IIb[12]—a syndrome distinct from multiple endocrine neoplasia, type II. Aside from the lack of mucosal neuromas or marfanoid habitus as in patients with MEN IIa, patients with MEN IIb rarely if ever have parathyroid gland involvement. Thus, three distinct syndromes have emerged, having in common neoplastic involvement of various endocrine glands (Table 1). The parathyroid glands are the only structures primarily involved in two of the syndromes. Crossovers between syndromes are extremely rare, but may occur, and will be discussed.

The propensity for each of the three syndromes is inherited as an autosomal dominant. However, expression of the genetic defect is variable. For example, in the MEN I syndrome, an affected parent may have parathyroid hyperplasia and a pituitary tumor, while an affected offspring might have just an islet cell tumor. Similarly, in families with MEN II, the affected parent could have a medullary thyroid carcinoma, while offspring might have any combination of medullary thyroid carcinoma, pheochromocytoma or hyperparathyroidism. Figure 1 gives an example of a family with MEN I and one with MEN II. It should be noted that patients with MEN I will not have MEN II components except by chance.

TABLE 1.—*Components of Multiple Endocrine Neoplasia (MEN) Syndromes*

Components	*Involvement in Affected Patients (Approximate Percent)*
MEN I:	
Parathyroid hyperplasia	90
Islet cell tumors	80
Pituitary adenomas	65
Others: Adrenal adenomas, thyroid abnormalities, thymomas, carcinoid tumors, multiple lipomata	Variable
MEN IIa:	
Parathyroid hyperplasia	40
Medullary thyroid carcinoma	95
Pheochromocytoma	50
MEN III or MEN IIb:	
Mucosal neuromas	100
Medullary thyroid carcinoma	95
Pheochromocytoma	50

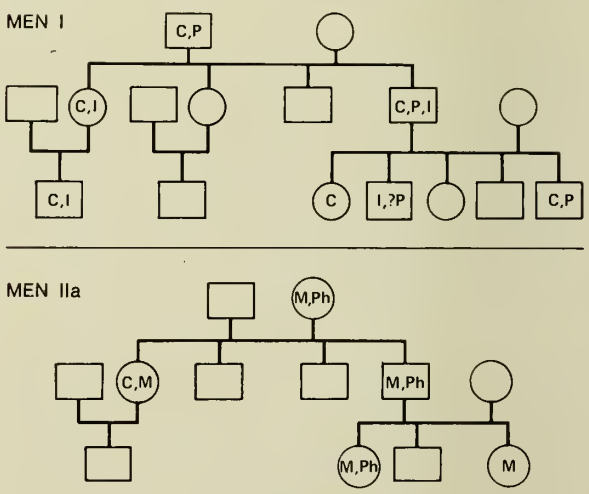

Figure 1.—Families with multiple endocrine neoplasia (MEN) I or MEN II syndrome. Open box = unaffected male; open circle = unaffected female; C = hyperparathyroid; P = pituitary tumor; I = islet cell tumor; Ph = pheochromocytoma, and M = medullary thyroid carcinoma.

Possible Causes of Multiple Endocrine Neoplasia Syndromes

As the multiple endocrine neoplasia syndromes constitute three distinct disorders, it is difficult to postulate a single mechanism to explain them. Several theories have been offered for the pathogenesis of the MEN I syndrome.

Mosaic Pleotropism

Wermer[4] suggested that there are mutant genes in all involved glands. Although this may be true,

it does not explain how affected persons in a single family could have involvement of different glands.

Nesidioblastosis

Vance[13] proposed that the primary defect in patients with MEN I was in the pancreatic islets. He called this nesidioblastosis, from the Greek word for islet building. The theory stipulates that an abnormality in the islets of Langerhans results in oversecretion of one or more hormones. Enlargement of other glands involved in the MEN I syndrome would be secondary to oversecretion of the islet cell hormone. For example, insulin hypersecretion might result in hypoglycemia. The hypoglycemia would induce growth hormone secretion and pituitary hyperplasia. Thus, chromophobe adenoma might occur.

Trying to explain parathyroid gland involvement is more difficult. However, one possibility is that insulin hypersecretion causes hypoglycemia, which results in epinephrine release. It is now relatively well accepted that epinephrine can stimulate parathyroid hormone (PTH) secretion.[14] Thus, parathyroid hyperplasia might ensue. Alternately, glucagon hypersecretion could result in calcitonin release, which could be followed by a compensatory parathyroid hormone release. The latter theory is improbable in that it is unclear that glucagon is a physiologic calcitonin stimulator. Nor is it certain that PTH hypersecretion necessarily follows calcitonin overproduction. The most obvious defect with the nesidioblastosis theory, however, is that many patients with the MEN I syndrome have been described as having pituitary and parathyroid gland involvement, while totally lacking in obvious islet cell hyperfunction.

Amine Precursor Uptake and Decarboxylation Concept

Weichert[15] and Pearse[16] have advocated a theory that explains some aspects of the multiple endocrine syndromes. It has been shown that pluripotential neural crest cells can migrate into the primitive foregut and be incorporated into developing endocrine glands. This has been well documented for the C cells of the thyroid. Neural crest or ventral neural ridge origin of cells of the pancreatic islets, gastrointestinal endocrine system, bronchial carcinoids, pituitary cells and adrenal medulla cells is suspected but unproved.[17] The neural crest cells maintain the ability of amine precursor uptake and decarboxylation (APUD). Although this theory may explain why cells of a specific endocrine gland, or cells of a tumor such as a bronchial carcinoid, can produce a variety of hormones, it does not clarify why in certain patients tumors of a variety of endocrine glands develop within defined familial patterns. Thus, while the APUD cell concept is exciting, the pathogenesis of the multiple endocrine neoplasia syndromes remains unknown. Furthermore, a neural crest origin for the parathyroid glands has not been shown.

MEN I Syndrome

The components of the MEN I syndrome are listed in Table 1 and will be reviewed.

Hyperparathyroidism

The parathyroid glands are involved in 80 percent to 90 percent of patients with MEN I.[5] Differentiating parathyroid adenomas from hyperplasia can be difficult. Therefore, there is no consensus regarding the pathologic features of the involved parathyroid glands. Ballard extensively reviewed all reported cases of MEN I-associated hyperparathyroidism for which pathology data were available. Of the cases, 33 percent were due to a single adenoma, 50 percent to multiple adenomas and 17 percent to hyperplasia involving all four glands.

Parathyroid hyperplasia may be asymmetric. Although four glands may be involved, one may be dominant. Its surgical removal could result in a transient return of serum calcium values to normal ranges. Because follow-up data are not available on all reported MEN I hyperparathyroid cases, it is difficult to know what percentage of patients had a recurrence of hyperparathyroidism after removal of a single abnormal gland. Although single or double adenomas may be seen in families with MEN I, I believe that further evidence will show that most affected hyperparathyroid patients have symmetric or asymmetric hyperplasia as well.

The clinical manifestations of hyperparathyroidism in patients with MEN I are extremely variable. Patients may be asymptomatic, or may have any combination of the serious complications of hyperparathyroidism, such as nephrolithiasis, bone disease, abdominal pain, depression or weakness.[18] Often the symptoms of hyperparathyroidism may be masked by the dramatic sequelae of accompanying tumor-related syn-

dromes, such as Zollinger-Ellison syndrome (ZES) or acromegaly. Alternately, the hyperparathyroidism may increase the seriousness of the symptoms of an accompanying tumor. It is well documented that hypercalcemia increases the gastrin levels in patients with the Zollinger-Ellison syndrome as well as elevating the potential for ulcers developing.[19]

Hyperplasia should be the suspected pathologic condition in all patients with MEN I-associated hyperparathyroidism, and in all hyperparathyroid patients who prove to have hyperplasia, studies should be done to rule out the MEN I syndrome. It may be that less than a fourth of patients with parathyroid hyperplasia will be shown to have components of the MEN I syndrome.[20] However, until there is a general consensus among pathologists as to what constitutes parathyroid hyperplasia, the exact incidence of the multiple endocrine neoplasia syndrome in this subpopulation remains unknown.

Islet Cell Tumors

Ballard reported islet cell tumors in 81 percent of the cases he reviewed.[5] The main secretory products of normal islet cells include insulin (β cells), glucagon (α cells) and somatostatin (δ cells).* Interestingly, the islet cell tumor most commonly seen in the MEN I syndrome is gastrin secreting. The normal islet does not contain gastrin.[21] Of Ballard's patients, 58 percent had ulcers. Although hyperparathyroidism itself may be associated with an increased incidence of ulcer disease,[22] the vast majority of the patients with ulcers probably had the Zollinger-Ellison syndrome.[23] Insulinomas are also common in the MEN I syndrome and the syndrome of watery diarrhea, hypokalemia and achlorhydria (WDHA) has also been associated. Glucagonomas, although rare, have been observed as well.

Occasionally, several of these syndromes have coexisted in the same patient, and a single islet cell tumor has elaborated a variety of hormones. Tumors secreting somatostatin have been described,[24] but have as yet been unassociated with the MEN I syndrome. The islet cell tumor syndromes will be reviewed.

Zollinger-Ellison Syndrome

The association of high gastric acid, multiple ulcers and pancreatic islet cell tumor is known as the Zollinger-Ellison syndrome.[23] Between 15 percent and 48 percent of patients with ZES are members of families with MEN I.[25-27] The pathologic features of ZES are no different in patients with MEN I than in sporadic cases. At least 60 percent of the islet cell tumors are malignant with metastasis to lymph nodes, liver and, occasionally, lung or skin; 30 percent are benign adenomas, of which at least 50 percent are multiple. Occasionally, diffuse hyperplasia of pancreatic islets is seen in the absence of, or in association with, a definite tumor. Approximately 10 percent of ZES cases result from a tumor in the duodenal wall.[28] Duodenal wall lesions, however, are more likely to be benign. ZES secondary to gastric antral hyperplasia[29] has never been associated with the MEN I syndrome.

The sequelae of ZES include diarrhea (33 percent), bleeding (40 percent), perforation (18 percent), emesis (25 percent) and ulcer pain (75 percent to 90 percent).[30] Some 75 percent of the ulcers are duodenal and 10 percent of these are multiple; 25 percent of the ulcers are in unusual locations, such as the jejunum.[30] Although gastric ulcers are seen in association with duodenal or jejunal ulcers, rarely are they present alone. Heartburn, a symptom of gastric reflux, is uncommon in ZES, and it is doubtful that this is related to gastrin's effect on increasing the tone of the esophagogastric sphincter.[31]

Diarrhea is seen in 30 percent to 75 percent of patients with ZES. Several theories have been advanced to explain this phenomenon. Gastrin, which is elevated in most cases of ZES, can cause a loss of fluid and electrolytes from the intestine.[32] However, because the diarrhea of ZES is relieved by nasogastric suction, and because removing stomach contents does not affect gastrin levels, it would seem that a direct role for gastrin in inducing the diarrhea is improbable. More likely, the diarrhea results from the effects of the large acid load. At low pH, lipase is inactivated,[33] bile salts are precipitated[34] and structural changes are induced in the small intestine.

The diagnosis of the Zollinger-Ellison syndrome can be made in several ways. Zboralske and Amberg[35] suggested that ZES was a diagnosis for radiologists. However, typical changes are seen in only 60 percent of cases. These changes include large gastric folds, a dilated and shaggy duodenum, single or multiple duodenal ulcers and areas of jejunal dilatation or ulceration.

Hypersecretion of gastric acid is common in

*α, β and δ cells are also called A, B and D cells.

ZES. Basal acid output is greater than 15 mEq per hour in two thirds of patients with ZES. However, similar findings are seen in 20 percent of patients with duodenal ulcers.[36] Histamine and gastrin are potent stimulators of gastric acid. Because gastrin is elevated in most persons with ZES, it was thought that exogenous gastrin or histamine would not produce significant increments in gastric acid output. In fact, the ratio of basal acid output to maximal acid output (histamine-stimulated or gastrin-stimulated) is greater than 0.6 in 75 percent of patients with ZES. This is a finding in only 4 percent of persons with duodenal ulcers. Therefore, stimulated acid testing is suggestive but not definitive in the diagnosis of ZES.

The 17-amino-acid polypeptide gastrin is hypersecreted by the islet cell tumors in virtually all patients with ZES. However, the secretion may be episodic. Thus, if a single determination is made, up to 25 percent of patients may appear to have a gastrin level within normal limits.[37] In most laboratories, a normal gastrin measurement is less than 200 pg per ml. However, patients with ZES frequently have values greater than 1,000 pg per ml. If other conditions that can elevate gastrin are eliminated (retained antrum syndrome, achlorhydria, intestinal obstruction and renal failure), then an elevated gastrin level is diagnostic of ZES. Because gastrin values are normal in 25 percent of ZES cases, various stimulatory tests have been devised. The calcium infusion test (5 mg of elemental calcium per kg of body weight per hour for three hours) was once the standard. Normal patients and those with duodenal ulcers may have a slight rise in gastrin, the peak response at three hours being less than 400 pg per ml. Values greater than 400 pg per ml are highly suggestive of ZES. Other rapid calcium infusion tests have been devised, but these have been supplanted by the secretin test. Secretin (1 to 2 units per kg of body weight given intravenously, as a bolus) will increase gastrin secretion in 70 percent to 85 percent of patients with ZES. Early reports[38,39] suggested that such an increase in response to secretin was specific for ZES. My own experience and that of others[40] does not confirm the specificity. That is, a gastrin response to secretin has been seen in association with achlorhydria and the retained antrum syndrome. However, the test remains very useful and is probably the best screening method for ZES.

Insulinoma

Insulinoma is the second most common type of islet cell tumor. The neoplastic β cells may elaborate insulin alone or insulin plus a variety of other hormones.[41] The clinical manifestations of an insulinoma have been well reviewed.[42] In sporadic cases of insulinoma, approximately 10 percent are due to multiple adenomas and 10 percent are due to islet cell carcinoma. In families with MEN I the vast majority of insulinomas are multiple, and β cell carcinoma is extremely rare.[5] The diagnosis of insulinoma is dependent on finding an inappropriately elevated insulin level in the presence of hypoglycemia. This can be accomplished by having the patients fast in the hospital and then monitoring their glucose and insulin levels. The diagnostic yield of fasting is 75 percent at 24 hours, 95 percent at 48 hours and 99 percent at 72 hours.[43] However, although fasting is diagnostically efficacious, it can be expensive. Therefore, other tests have been devised. Tolbutamide can induce both a dramatic increase in the level of insulin, and hypoglycemia in patients with insulinoma. However, the test is somewhat nonspecific and can be dangerous.[44]

An interesting approach has been advanced by Turner.[45] Fish insulin does not cross-react in a radioimmunoassy with human insulin. When patients are given sufficient fish insulin, hypoglycemia is induced. Patients without insulinoma will have low endogenous levels of insulin in response to the hypoglycemia. Patients with insulinoma will continue to have inappropriately elevated levels of human insulin. The fish insulin test can be extremely useful in screening patients; however, fish insulin is not generally available.

Another approach to the diagnosis takes advantage of our knowledge of insulin secretion. The β cell makes proinsulin, some of which is secreted into the circulation. Most of the proinsulin, however, is cleaved within the islet cell into insulin and the connecting peptide (C peptide). C peptide and insulin are secreted into the circulation in a 1:1 molar ratio. In normal persons, proinsulin constitutes less than 15 percent of circulating insulin levels. However, in some patients with insulinoma, proinsulin constitutes greater than 20 percent of circulating insulin.[46] A modification of the fish insulin test takes advantage of the fact that C peptide does not cross-react with insulin in radioimmunoassays. When

bovine insulin is given to normal controls, hypoglycemia is induced and C peptide secretion is inhibited. Thus, the level of circulating C peptide coincident with the hypoglycemia would be very low. Patients with insulinoma may have an inappropriately elevated level of C peptide.[47]

WDHA Syndrome

In 1958 Verner and Morrison[48] described a syndrome of severe watery diarrhea, hypokalemia and achlorhydria (WDHA) associated with islet cell adenoma of the pancreas. One of their original cases was a member of a family with MEN I. The syndrome can clearly be differentiated from ZES by a lack of hyperacidity and the presence of normal gastrin levels. Diarrhea in these patients can be life-threatening, with 6 to 10 liters of fluid being lost per day. The hypokalemia is secondary to intestinal electrolyte loss. The achlorhydria need not be absolute. Some of these patients have hypercalcemia, which remits with removal of the islet cell tumor. The pathogenesis of the hypercalcemia is unclear.[49] Similarly, abnormal glucose tolerance or overt diabetes has been seen. This condition may respond to correction of the potassium abnormalities.

The hormone secreted by the islet cell tumor remains unknown. Secretin[50] and gastric inhibitory polypeptide (GIP)[51] have been suggested but, seemingly, discarded. Vasoactive intestinal peptide (VIP) has been advocated as the causative hormone by several authors.[52,53] However, the controversy continues.[54,55]

Glucagon-Secreting Tumors

Glucagon-secreting tumors are rare, but have been associated with the MEN I syndrome. The main features include a debilitating skin rash (migratory necrolytic erythema), weight loss, anemia, vitamin-resistant stomatitis and mild glucose intolerance.[56,57] Diagnosis can be made by discovering inappropriately elevated glucagon levels in association with a glucose challenge.[58] Somatostatin-secreting tumors, which can present with diarrhea and diabetes, are as yet unassociated with the MEN I syndrome.[24] Therapy for islet cell tumors in general is reviewed below.

Pituitary Abnormalities

Pituitary adenomas were present in 65 percent of the patients reviewed by Ballard.[5] With the diagnosis of pituitary tumors rendered more sensitive by sellar tomography, the incidence may be higher. In Ballard's series, most tumors were nonsecretory or so-called chromophobe adenomas. Growth hormone hypersecretion with consequent acromegaly was the most common pituitary tumor hormone-related syndrome. With the advent of the prolactin radioimmunoassay,[59] we have learned that many of the "chromophobe adenomas" are prolactin-secreting tumors. Prolactinomas in association with MEN I have been described.[60,61] To date no examples of tumors that secrete thyroid-stimulating hormone (TSH), luteinizing hormone (LH) or follicle-stimulating hormone (FSH) have been found in association with the MEN I syndrome. Adrenocorticotrophic hormone (ACTH)-secreting pituitary tumors in persons with MEN I are rare. However, Cushing syndrome in association with the MEN I syndrome is not uncommon. It can be caused by an adrenal adenoma, or result from ectopic ACTH production by bronchial or abdominal carcinoid tumors,[62] thymomas[63] or islet cell adenomas.[64]

Other Associations With MEN I

Adrenal adenomas or carcinoma may have an increased incidence in persons with MEN I.[5] The association is somewhat tenuous and, although physicians caring for such patients should consider adrenal cortex abnormalities, they will not be reviewed here. Similarly, although thyroid abnormalities, such as follicular adenomas or Hashimoto thyroiditis, may be more common in patients with MEN I, their high frequency in the general population renders a clear association with MEN I difficult. Bronchial and abdominal carcinoid tumors are more common in persons with MEN I than in the general population.[5] In patients with MEN I a typical carcinoid syndrome may be noted.[65] However, the carcinoid tumors are capable of elaborating a variety of hormones that can, in turn, induce myriad symptoms. Also, there is an increased incidence of secretory, or nonsecretory, thymomas.[5] Multiple lipomata were seen in 11 of Ballard's 84 reviewed cases. These tumors are usually asymptomatic but can be massive and, occasionally, retroperitoneal.[66] Whether the lipomatous tumors constitute a part of the MEN I syndrome or are secondary to a coinherited gene, can be questioned. I have seen two patients (50 and 60 years old) from families with MEN I, who had multiple lipomata but no evi-

dence of any of the other components of the MEN I syndrome.

Screening for the MEN I Syndrome

Who should be screened? Because MEN I involves an autosomal dominant inheritance, parents, siblings and offspring of affected patients should be screened. Screening should also be considered in any patient in whom a single component of the MEN I syndrome is noted. Because testing can be expensive, the number of tests done should depend on each patient's clinical history. For example, patients with pituitary tumors should be carefully questioned as to symptoms of hyperparathyroidism or islet cell tumors. Similarly, patients with hyperparathyroidism need to be questioned for symptoms of pituitary hormone hyposecretion or hypersecretion, as well as islet cell abnormalities. Patients with proved parathyroid hyperplasia require hormonal screening for both MEN I and MEN II syndromes.

MEN I is so common in patients with ZES that at the least a serum calcium test and x-ray studies of the sella turcica should be done. A similar approach may be taken in patients with insulinoma. The tumors of MEN I syndrome have been diagnosed in patients 7 to 83 years old. Therefore, screening is recommended once a year or biannually in patients 7 years old or older. Table 2 outlines an outpatient screening approach to asymptomatic patients. The diagnostic approach to patients with symptoms of specific endocrine tumors has been previously reviewed.

Therapy for MEN I Syndrome

Therapy for the MEN I syndrome is, of course, dependent on the number and type of tumors present. Patients with hyperparathyroidism, because of the high incidence of parathyroid hyperplasia, should be treated by removal of 3 or 3½ of the glands. Pituitary tumors, when diagnosed early, can usually be removed safely by a transsphenoidal microsurgical procedure. Insulinomata, because of the high frequency of multiple tumors, are best treated by total or nearly total pancreatectomy. When pancreatectomy is impossible, or noncurative (islet cell carcinoma), administration of diazoxide,[67] streptozocin,[68] or mithramycin[69] may be efficacious.

The Zollinger-Ellison syndrome represents the most difficult therapeutic problem. Total gastrectomy without pancreatic exploration has been advocated as the therapy of choice. More than 90 percent of patients with ZES who survive a total gastrectomy are still alive after five years.[70]

TABLE 2.—*Outpatient Screening for Asymptomatic Persons in Families With Multiple Endocrine Neoplasia I*

- Measure calcium and phosphorus levels after fasting, and parathyroid hormone level if calcium is elevated.
- Measure serum glucose level after 12-hour fast, and serum insulin level if glucose is less than 60 mg per 100 ml.
- Measure gastrin level. Administer 2 units per kg of secretin intravenously over 30 seconds. Measure plasma gastrin level at 0, 2, 5, 10 minutes.
- Obtain a sellar tomogram. Carry out specific pituitary function tests if clinically indicated.

It has been suggested that total gastrectomy could result in diminution of tumor size,[71] but apparently this theory has not stood the test of time. Nevertheless, the operation removes the source of acid secretion, thus eliminating the main cause of morbidity and mortality of the syndrome. Cimetidine, an agent that blocks the H_2 receptor has been used with some success in patients with ZES.[72] Although certain patients become refractory to the agent,[73] cimetidine probably merits a trial before total gastrectomy is done in some patients with mild disease.

With the advent of early screening for ZES, some MEN I family members are found to have the syndrome while being asymptomatic.[74] Whether these patients should be radiologically evaluated for resection of the tumors, treated with cimetidine or have a prophylactic total gastrectomy is as yet undecided. In patients with hyperparathyroidism and ZES, the parathyroid disease should be treated first. This may result in both a lowering of gastrin levels and amelioration of ulcer symptoms. It should be noted, however, that although hyperparathyroidism can itself cause a slight elevation of serum gastrin, values greater than 400 pg per ml in the absence of gastrin-elevating conditions are probably diagnostic of ZES. The fall in gastrin following a parathyroid operation is only transient, and the symptoms and signs of ZES, as well as the elevation of gastrin levels, will recur.[75]

MEN II Syndrome

The components of MEN II include medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism (Table 1). Hyperparathyroidism is seen in less than 50 percent of cases. As in patients with MEN I syndrome, it is usually due to parathyroid hyperplasia. Whether the

parathyroid hyperplasia is secondary to an inherited defect or is a response to calcitonin hypersecretion is questioned. PTH levels are only marginally elevated,[76] if at all,[77] in association with medullary thyroid carcinoma; and there does not appear to be an increased incidence of hyperparathyroidism in association with sporadic medullary thyroid carcinoma. Thus, an inherited defect causing hyperparathyroidism is probable. Evaluation of and therapy for hyperparathyroidism are similar to those in the MEN I syndrome.

Medullary Carcinoma of the Thyroid

Medullary carcinoma of the thyroid (MCT) constitutes approximately 5 percent of all surgically removed thyroid tumors. Of the tumors, 75 percent are sporadic in nature, with a peak incidence occurring in persons 40 to 60 years old; 25 percent are familial in association with the MEN IIa or IIb syndrome.[78] The tumor consists of regular nests of eosinophilic granular cells with varying degrees of atypical cell structure and calcification. Differentiating it from other thyroid tumors would be difficult, except for the universal presence of amyloid. The nature of the amyloid is still undecided, but there may be some homology between the polypeptide structure of the amyloid fibrils and parts of the calcitonin molecule.[79] Although most sporadic MCT cases are unilateral, well-established familial cases of MCT are most often bilateral.[77] The tumors are usually found in both thyroid lobes at the junction of the middle and upper third. This corresponds to the area of greatest concentration of C cells in normal thyroid glands. Recently, with earlier diagnosis, a few familial unilateral cases have been discovered.[80] However, because these patients had total thyroidectomies, we will not know if with time a tumor would have developed on the opposite side.

Calcitonin radioimmunoassay, to be discussed below, has made early diagnosis of MCT possible. A premalignant condition of C cell hyperplasia has been described in affected MEN II family members.[81] The familial tumors may develop in persons any time after the age of 7. MCT, whether sporadic or familial, has variable malignant potential. Metastasis to local lymph nodes, liver, bone and lung has been described.[78] However, after removal of tumors before lymph node metastatic lesions have appeared, patients survive an average of 12 years, not different from the actuarial norm for the general population. Once lymph node metastatic lesions have occurred, the 12-year survival is 40 percent of normal survival.

MCT may be totally asymptomatic. It may present as a painless thyroid nodule. Approximately 5 percent of patients have diarrhea as the chief complaint, but in 25 percent diarrhea will develop in the course of the disease. Other symptoms of MCT are associated with the tumor's secretion of hormones other than calcitonin. Cushing syndrome, secondary to hypersecretion of ACTH by medullary carcinoma, is well known.[77]

The pathogenesis of diarrhea in MCT remains unknown. Calcitonin is universally elevated in patients with this tumor, and can decrease intestinal fluid and electrolyte absorption. However, there is little correlation between the presence or absence of diarrhea and the level of calcitonin. Release of prostaglandins by the tumor has been implicated as causative of diarrhea,[82,83] and, occasionally, the diarrhea has been controlled by prostaglandin synthetase inhibitors.[84] However, a definite role for prostaglandins has not been established. Although the symptoms of MCT bear some resemblance to those of the carcinoid syndrome, levels of serotonin are normal. Vasoactive intestinal polypeptide (VIP) has been elevated in some patients with MCT and diarrhea,[85] but not in others (Pont and Potts, unpublished data, 1980).

The 32-amino-acid polypeptide calcitonin is secreted by the ultimobranchial body of lower species and by the C cells of the thyroid in mammals. The C cells, or parafollicular cells, are of neural crest origin. The APUD cell concept, previously discussed, may explain both the association of medullary thyroid carcinoma and pheochromocytoma, and the ability of C cells to secrete a variety of hormones. With one exception, every medullary thyroid carcinoma heretofore described, secretes calcitonin. However, in many laboratories calcitonin assays are insensitive, and hormone secretion may be episodic. Therefore, 25 percent of patients with MCT may appear to have a normal calcitonin level on a single plasma determination. Physiologic secretagogues for calcitonin remain questionable.[86] Both calcium and gastrin are potential physiologic stimulators of calcitonin secretion, and have proved to be potent pharmacologic secretagogues. Either calcium or pentagastrin infusion can be expected to cause a minimal elevation of calcitonin in unaffected persons. In 95 percent of patients with MCT a dramatic rise in the level of

TABLE 3.—*Stimulatory Tests of Calcitonin* for the Diagnosis of Early Medullary Carcinoma of the Thyroid*

Infusion Tests	*Procedure*
Pentagastrin	Administer 0.5 μg/kg of body weight intravenously; measure serum calcitonin level at 0, 2, 5, 10, 20 minutes (95%).
Calcium (long)	Administer 5 mg/kg of body weight per hour intravenously for three hours; measure serum calcitonin level at 0, 1, 2, 3, 4 hours (95%).
Calcium (short)	Administer 2 mg/kg of body weight intravenously in 1 min; measure serum calcitonin level at 0, 2, 5, 10, 20 minutes (95%).
Calcium (intermediate)	Administer 3 mg/kg of body weight in 10 minutes; measure serum calcitonin level at 0, 10, 20, 30, 60 minutes (95%).

*Peak calcitonin value greater than 1 ng/ml is diagnostic. (Diagnostic peak levels vary among different laboratories.) Time of usual peak is underlined. Diagnostic accuracy in parentheses.

calcitonin in response to either stimulus occurs, and in approximately 75 percent there will be a significant rise of calcitonin in response to alcohol taken orally.[87] The screening for medullary carcinoma is reviewed by Deftos[88] and is outlined in Table 3. The main side effect of calcium infusion is transient nausea. Alcohol is happily tolerated. Pentagastrin may cause abdominal or chest pain. It may also induce a vasovagal-like reaction, lasting two to ten minutes. Administering the pentagastrin with the patient in the Trendelenburg position often eliminates this unpleasant side effect.

Histaminase is often secreted by MCT.[89] However, calcitonin is usually a better tumor marker.

Despite the occasional presence of unilateral tumors in familial MCT, therapy should consist of a total thyroidectomy. The posterior capsule of the thyroid may be left intact so as to preserve parathyroid function. Preliminary screening should establish the presence or absence of hyperparathyroidism before the operation is done.

Surgical therapy should never be undertaken until pheochromocytoma has been ruled out or the tumors surgically removed. When calcitonin remains elevated after removal of bilateral medullary thyroid carcinomas, therapeutic approach becomes difficult. Conditions other than MCT associated with calcitonin elevation must be ruled out. These include acute and chronic renal failure, maternal and fetal plasma at term, pyknodysostosis, hypergastrinemic states and malignant tumors (especially of the breast, lung and prostate.)[88,90] If the most likely cause of the elevated calcitonin is residual MCT, little can be done. Venous catheterization with calcitonin sampling can occasionally locate one or several sites of residual tumor.[91] However, the return of calcitonin values to normal ranges that is induced by removal of affected nodes can be expected to be transient, and recurrent disease may soon become apparent (Pont and Potts, unpublished data, 1980). Consistently effective chemotherapy for metastatic medullary thyroid carcinoma is unavailable. Because the tumor may have an asymptomatic and relatively benign course, patients can be carefully observed.

Pheochromocytoma

More than 50 percent of affected persons in families with MEN II will have a pheochromocytoma. Approximately 90 percent of patients with pheochromocytoma have sporadic disease; that is, conditions unassociated with MEN II or one of the neurocutaneous syndromes (such as tuberous sclerosis, von Hippel-Lindau or von Recklinghausen disease). In the sporadic cases, 80 percent of pheochromocytomas are due to a solitary adrenal lesion; 10 percent to extra-adrenal disease along the sympathetic chain (99 percent within the abdominal cavity), and 10 percent are due to bilateral or malignant disease, or both. Greater than 50 percent of pheochromocytomas in association with MEN IIa or IIb are bilateral. The incidence of extra-adrenal disease is similar to that of sporadic cases. Metastatic disease is extremely uncommon in association with the MEN syndromes. Fewer than five cases have been described.[92] Therefore, a rule of thumb is that when a surgeon removing an MEN-associated pheochromocytoma finds metastasis to the liver, he is probably dealing with metastatic medullary thyroid carcinoma. Screening of families with MEN II has detected some patients with elevated catecholamine levels, but without a definitive adrenal medullary or extra-adrenal tumor. These patients have been found to have adrenal medullary hyperplasia.[93,94]

The symptoms of pheochromocytoma are related to hypersecretion of catecholamines. The combination of symptoms found in familial cases is no different than that of sporadic cases. Early screening may detect asymptomatic patients. Alternately, the classic triad of headaches, sweating and palpitations may bring the patient's condition to attention. Hypertension and hypertensive crises are the main dangers of pheochromo-

cytoma. However, in only 25 percent of cases is the hypertension truly paroxysmal. In 30 percent the hypertension is sustained but there are superimposed paroxysms; 35 percent of patients have sustained hypertension and no crises. Ten percent of patients have no hypertension.[95,96]

Catecholamine hypersecretion by these tumors makes diagnosis of the disease straightforward. The tumors secrete both norepinephrine and epinephrine. The catecholamines are metabolized both within and without the tumors to vanillylmandelic acid (VMA) and metanephrine. In patients with sustained hypertension, values for total urinary catecholamines, VMA and metanephrine should all be elevated. In patients with paroxysms of hypertension collection of urine during and after the paroxysm may be required to determine elevated values. An elevated 24-hour measurement of urine metanephrine in the absence of ingestion of exogenous catecholamines or monoamine oxidase inhibitors is probably the best single test for pheochromocytoma.[97] VMA values are almost as reliable.

Urinary catecholamines may be especially helpful in diagnosing patients with small tumors. These tumors may lack the ability to catabolize norepinephrine and epinephrine. Thus, urinary values of the latter substances may be elevated while those for VMA and metanephrine may be normal. In normal persons, urinary epinephrine constitutes less than 20 percent of excreted free catecholamines. Tashjian[77] has shown that in some patients with MEN II having small pheochromocytoma lesions, there are elevated urinary epinephrine to norepinephrine ratios. The diagnostic value of plasma catecholamines[98] remains undetermined. Histamine, tyramine or glucagon stimulation tests are not usually efficacious in recognizing MEN II. The radiologic assessment of patients with biochemically proved pheochromocytoma is very useful. Intravenous pyelography is of limited value. Arteriography is usually diagnostic, but represents a hazard for patients. The dangers of the procedure can be lessened by preparing patients for arteriography as one would for a surgical procedure. Recently, computerized axial tomography (CAT) of the abdomen has been effective in locating tumors.[99] The procedure is safe and should be done before arteriography is considered.

Collecting selective blood specimens for catecholamine assay has been advocated for determining the location of extra-adrenal disease. Although useful, this procedure may be unnecessary in patients in whom a proper CAT scan of the abdomen has been done.

Recently, the preoperative and postoperative management of patients with pheochromocytoma has been reviewed.[95] With adequate preoperative preparation, the surgical risks are small. Because of the frequency of bilateral disease, an abdominal approach should be taken. When bilateral tumors are found, bilateral adrenalectomy is essential. Whether bilateral adrenalectomy should be done in cases of unilateral disease is questionable. If adequate follow-up is assured, removal of the involved adrenal gland and biochemical screening every three to six months may be adequate therapy.

MEN III Syndrome (MEN IIb)

The components of the MEN III syndrome include multiple mucosal neuromata, a marfanoid habitus, medullary thyroid carcinoma and pheochromocytoma. Hyperparathyroidism is rarely seen.[11,12] Patients are of normal intelligence and do not have the hyperextensible joints frequently seen in association with the Marfan syndrome. They have a classic facies with a flat nose bridge, and large lips. Mucosal neuromata can be pathologically differentiated from neurofibromata.[12] Patients with MEN IIb do not have café au lait spots. The neuromata are seen on the lips, tongue, buccal mucosa, eyelids, conjunctivas and skin, and along the gastrointestinal tract. Slit lamp examination may disclose hypertrophied corneal nerve fibers. The gastrointestinal neuromata can result in either diarrhea or severe constipation.

The pathologic expression of the pheochromocytoma and medullary thyroid carcinoma is similar in the MEN IIb and MEN IIa syndromes. The presence of multiple neuromata in association with MCT and pheochromocytoma lends further credence to the neural crest hypothesis.

In more than half the patients with the MEN IIb syndrome, the incidence proved to be sporadic. However, the typical phenotypic appearance should result in screening of both affected patients and family members. An outline of outpatient screening for MEN IIa and IIb patients is provided in Table 4.

Mixed Syndromes

The MEN I and MEN II syndromes appear to be distinct entities. Hyperparathyroidism may be seen in both. Cushing syndrome is seen in both

TABLE 4.—*Outpatient Screening for Multiple Endocrine Neoplasia IIa and IIb Syndromes**

Measure calcium level after fasting.
- Normal—rescreen patient after a year.
- Elevated—diagnostic of hyperparathyroidism (calcium level may, occasionally, return to normal ranges after removal of a pheochromocytoma[104]).

Measure calcitonin level after fasting.
- Normal—Administer pentagastrin test and/or calcium test (see Table 3).
- Elevated—diagnostic of medullary thyroid carcinoma.

Analyze two 24-hour urine specimens to determine levels of vanillylmandelic acid, mentaephrine, catecholamines and creatinine. (Patients collect the two urine specimens in acid bottles, 15 ml HCl solution.)

*Screening to be done yearly for patients 7 years and older.

syndromes, but is explainable by ectopic secretion of ACTH. Of late, some questionable crossovers of the syndrome have been described. In bulls, ultimobranchial calcitonin-secreting tumors have been found in association with pituitary acidophilic adenomas.[100] In humans, neurofibromatosis has been described in association with the Zollinger-Ellison syndrome[101] and an adrenocortical adenoma.[102] Because neurofibromatosis (von Recklinghausen disease) is not truly a component of MEN II, the association may be serendipitous. Similarly, the appearance of a chemodectoma in a patient with a classic MEN I syndrome[103] may represent a chance occurrence.

Summary

The components of three distinct multiple endocrine neoplasia syndromes have been described. Early screening and therapy for potentially affected family members is stressed as an important means of intervening before clinical sequelae ensue.

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Specialty Conference

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An edited transcription of an Interdepartmental Clinical Case Conference arranged by the Department of Medicine, UCLA School of Medicine, Los Angeles, California.

Kidney Stones

The prevalence of kidney stones has steadily risen during this century; passage of a calculus and a positive family history increase the probability of recurrence. Findings from recent studies on the cause of renal calculi have stressed crystallization and crystal aggregation of stone minerals from supersaturated urine, rather than excessive organic matrix. Absence of normal urine inhibitors of calcium salts is also stressed. Formation of calcium oxalate stones is the major problem. Therapy with decreased calcium and oxalate intake, thiazides, phosphate salts and allopurinol in various combinations has substantially decreased the prevalence of recurrent stones. The rationale for the use of allopurinol is that uric acid salts enhance the tendency for calcium oxalate to crystallize from supersaturated urine. The hypercalciuria seen in 30 percent to 40 percent of patients with oxalate stones is usually caused by intestinal hyperabsorption of calcium. Although patients with uric acid calculi constitute only a small fraction of those in whom stones form, they represent a group in whom good medical therapy, based on sound physiologic principles, has proved extremely successful. Renal tubular syndromes lead to nephrocalcinosis and lithiasis through hypercalciuria, alkaline urine and hypocitraturia, the latter an inhibitor of calcium salt precipitation. Recent advances in surgical techniques are discussed, including the rationale for removing staghorn calculi. The ileal ureter and coagulum pyelolithotomy deserve special emphasis.

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CHARLES R. KLEEMAN, MD:* During this century there has been a steady rise in the prevalence of upper urinary tract stones[1]; however, the precise incidence in any but the smallest communities has never been determined.[2] A recent study (which may have general applicability) by Ljunghall and Hedstrand[3] is a retrospective analysis of the natural history of upper urinary tract stones in ambulatory middle-aged men in an urban population (Uppsala, Sweden). The incidence of stones in 2,322 men was 13.7 percent. This figure was based on four criteria: (1) spontaneous passage of a stone noted by the patient, (2) operative removal of a stone, (3) a stone or stones of the upper urinary tract shown on x-ray films and (4) characteristic clinical findings judged by a physician at the time of the symptoms.

Despite the availability of excellent hospital facilities in the community, only 23 percent of these men had on any occasion been admitted to hospital. Hospital statistics, therefore, cannot be relied on for determining the prevalence of nephrolithiasis. Ljunghall and Hedstrand[3] presented incidence statistics available in the literature from other Scandinavian countries, the United States and Great Britain: the incidence varied from 3.5 percent to 13.7 percent, with an average of 7 percent. In the population they studied, they noted a progressive increase in the total number of patients with kidney stones during each five-year period, beginning with those less than 19 years old to those 50 years old. In about 42 percent of patients there had been at least one recurrence of stones by age 50; the risk of relapse increased progressively after five years from 31.5 percent to 72 percent in patients who had their first stone attack more than 20 years previously. Therefore, formation of kidney stones is not a singular event but a process in which the risk of recurrence remains for many years. Studies of large series have also failed to distinguish persons apt to have recurrent stones from those in whom stones occurred only once (with regard to biochemistry of serum and urine, composition of stone, urinary infection or need for surgical operations).[3] Ljunghall and Hedstrand[3] found that a positive family history was significantly correlated with multiple recurrences, and that, as other investigators had noted,[4-6] a family history of kidney stones is more common for patients with stones than for persons in a control population. This has been attributed to both environmental and genetic factors[3-6] that predispose a person to the formation of renal calculi.

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Pathogenesis

Although it is not possible to indicate the exact pathogenesis of kidney stones in most patients, the situation is not hopeless. It is possible to set up an orderly scheme that will include all or almost all of the fundamental pathogenic factors involved in the formation of a clinically evident renal calculus, and apply it to patients.[7] Figure 1 by Vermeulen[7] represents diagrammatically all

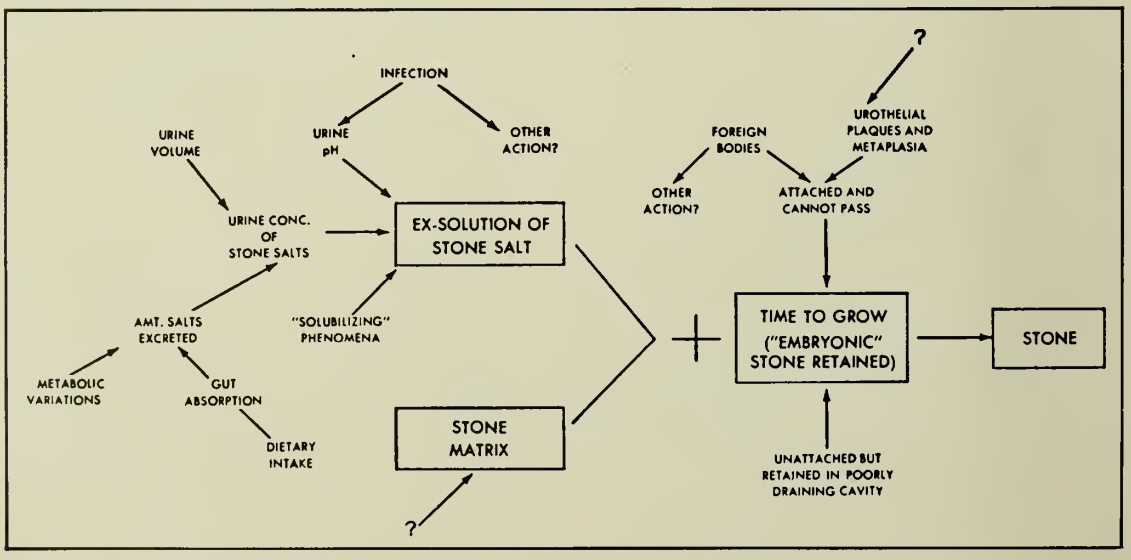

Figure 1.—Summary view of factors cooperating in urinary stone formation. (From Vermeulen[7]; reproduced by permission from University of Chicago Press.)

the known factors involved in urinary stone formation. The final stone at the far right in the diagram represents any type of renal calculus. To the left, the concentration of the salt (or salts) or compound making up the stone is a function of the amount excreted and the rate of urine flow. The amount excreted depends on the dietary intake, its absorption by the gut and metabolic (endogenous) factors responsible for its formation, such as uric acid, or enhanced renal excretion (decreased tubular reabsorption of cystine).

It is axiomatic that the larger the urine volume, the lower will be the concentration of the constituents of the stone, and the less the propensity for crystallization from a supersaturated solution (and vice versa).[8,9] Hodgkinson[10] reported that cystine, uric acid and magnesium ammonium phosphate stones are readily explained in these terms: cystine stones are caused by oversaturation of the urine with cystine; uric acid stones by excessive excretion of uric acid or excessive urinary acidity (both of which lead to oversaturation of the urine with uric acid), and magnesium ammonium phosphate stones by liberation of ammonium ions from urea. This occurs by urea-splitting organisms leading to a rise in urine pH and oversaturation of the urine's content of magnesium ammonium phosphate. Thus, urine concentration, infection and urinary pH (Figure 1) are important factors in the crystallization of a supersaturated solution. The degree of saturation of a solution is determined by comparing the ionic activity product with the known solubility and formation products of the relevant solute. Solutions having activity products below the solubility product are said to be undersaturated and any crystals of the solute will tend to dissolve. Above the solubility product, there is a region of metastable supersaturation in which a solution can exist for relatively long periods without crystallization occurring, although formation of crystals can be induced by the addition of a suitable nucleus. Above the formation product, spontaneous nucleation can occur and crystal growth is usually rapid.[10]

The above principles have been applied for many years to studies of the solubility of the major divalent ion salts and other stone-forming

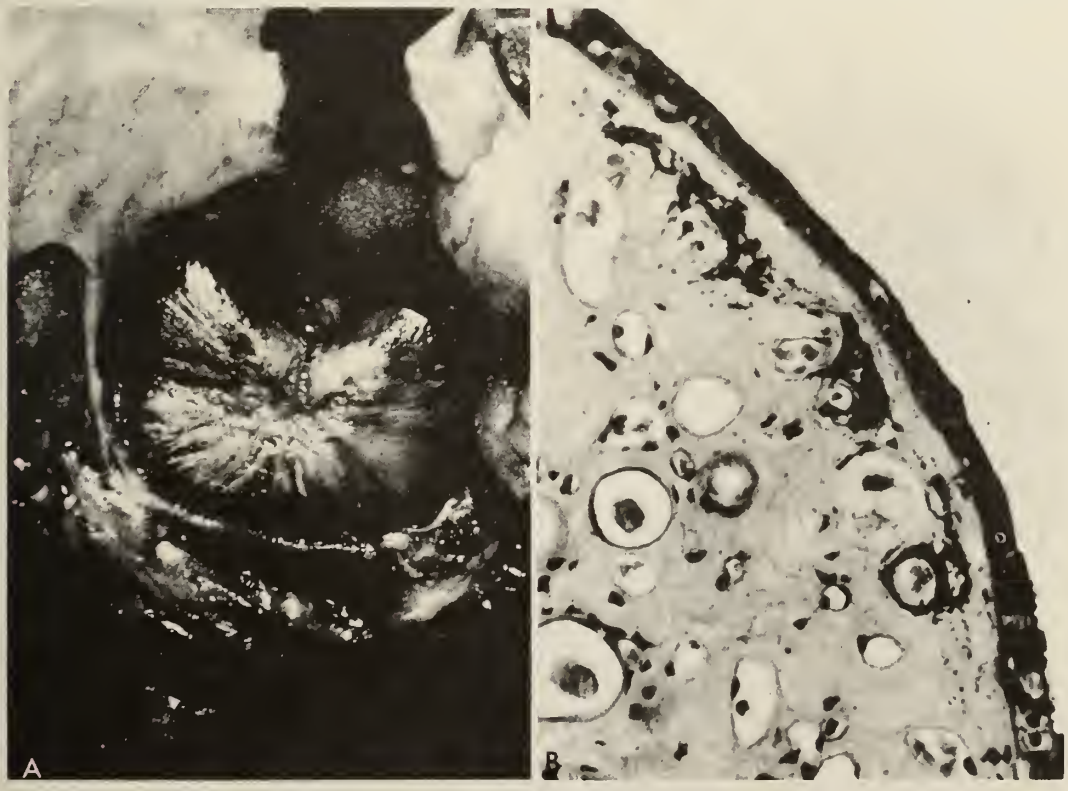

Figure 2.—Randall plaques. **A**, Papilla with Randall plaques viewed from above. **B**, Section of a Randall plaque showing calcification around capillaries in subepithelial plane (Hematoxylin and eosin stain; reduced from magnification ×250). (From Burry et al[19]; reproduced by permission from Human Pathology.)

solutes in human urine.[7-12] They have shown that normal urine contains potent inhibitors of calcium oxalate and calcium phosphate crystal growth, one or more of which may be deficient in the urine of persons in whom stones form.[9-13] Vermeulen[7] refers to these inhibiting substances as "solubilizing" phenomena or materials that by their presence impede or prevent stone salts from passing from the dissolved to the solid state, termed "ex-solution" (Figure 1). Citrates, pyrophosphates, magnesium and phosphocitrates[12] have been shown to have considerable inhibiting properties in the concentrations usually found in human urine. However, taking each separately, it is not clear whether their concentrations in urine differ significantly between persons in whom stones form and those in whom stones do not form. Despite this, the urine of a patient with calcium oxalate stones, the most common type of kidney stone in the Western world, is deficient in urinary-inhibiting activity against crystallization of calcium oxalate.[10,11]

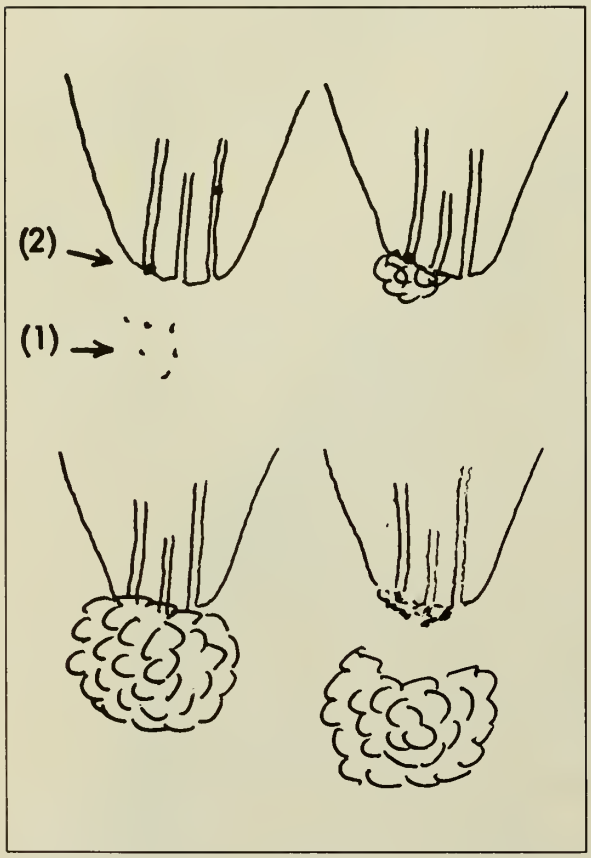

Figure 3.—Schematic representation of embryogenesis and crystal growth on renal papilla beginning with formation of potential embryonic stones in collecting ducts. Many abort into pelvis (1), but one is shown caught at duct ostium (2). Retained embryonic stone, now exposed to pelvic urine, continues to grow and finally sloughs away or fragments. (From Vermeulen et al[18]; reproduced by permission from Journal of Urology.)

In Vermeulen's diagram (Figure 1) organic matrix of the stone is given a prominent position because some nidus of proteinaceous material, even of a minimal amount (5 percent of the stone's weight), is found in almost all of the common renal stones.

This organic material may be derived from the site on the renal pyramid or calyx where the initial abnormal crystallization or crystal aggregation is occurring.[7,8,14] Oversaturation of the urine with certain chemical constituents and defective inhibitory activity provide a rational explanation for the nucleation and a subsequent growth of many submacroscopic or embryonic stones.[9-14] However, it is difficult to conceive of the stone growing to macroscopic size simply de novo in the free flowing urinary stream. More likely, a site of microscopic tissue degeneration or abnormality on either the tip of the medullary pyramid or on the minor calyceal epithelium, serves as the organic nidus to which the crystals will adhere, and grow to sufficient size without being washed "downstream and out" in the excreted urine.[7,8,14] Time is also a factor (Figure 1): "A stone obviously requires time to grow to significant size and it can so grow only if it is retained in the urinary tract."[7]

Many years ago Randall[15-17] developed a concept relating growth of the embryonic stone to the renal papilla. Vermeulen and associates[18] summarized Randall's concept and we quote from their paper:

> According to his view, the stone process could begin in a seemingly normal urinary tract only because an unrecognized abnormality was, in fact, present—an antecedent lesion of the renal papilla. In a series of more than 1,100 autopsies he found minute surface patches or plaques on the papilla in more than 19 percent of the kidneys examined. He concluded that these surface defects acted as stone growth centers since small stones were occasionally attached to them. Randall believed that the plaques were small areas of subepithelial calcification; perhaps the result of antecedent infection, a toxic agent, or some kind of minute vascular disturbance leading to necrosis beneath the urothelium. Later the plaque was denuded of its epithelial covering so that the calcified tissue was now exposed to the pelvic urine and could behave as a foreign surface attracting crystallization and stone formation upon itself.

Subsequent publications have confirmed Randall's findings and, most recently, Burry and colleagues[19] reviewed the entire subject and presented

additional confirming data. Figure 2[19] shows the gross and microscopic appearance of the plaques discussed by Randall in the human kidney. Figure 3 offers a schematic representation of embryogenesis and growth on renal papilla; Figures 4 and 5 illustrate clinical findings of stone formation.[18]

The final product of the metabolic, physiochemical and abnormal cooperating factors, the clinically evident stone (Figure 1), may appear as an asymptomatic finding on a kidney, ureter and bladder (KUB) study or on an intravenous pyelogram (IVP) done for other purposes. These might include a diagnostic follow-up of abnormal urinary sediment; an attack of renal colic; an episode of gross hematuria or acute urinary tract infection, or part of a clinician's workup of a patient with positive risk factors for nephrolithia-

Figure 4.—Small human oxalate calculi. **A** and **B**, Concave surfaces suggest formation upon papillary tip. **C**, Central crystalline pedicle (oxalate) within concavity. **D**, A larger stone with central dimple and small pedicle; white material in dimple is apatite (measuring bars equivalent to 1 mm). (From Vermeulen et al[18]; reproduced by permission from Journal of Urology.)

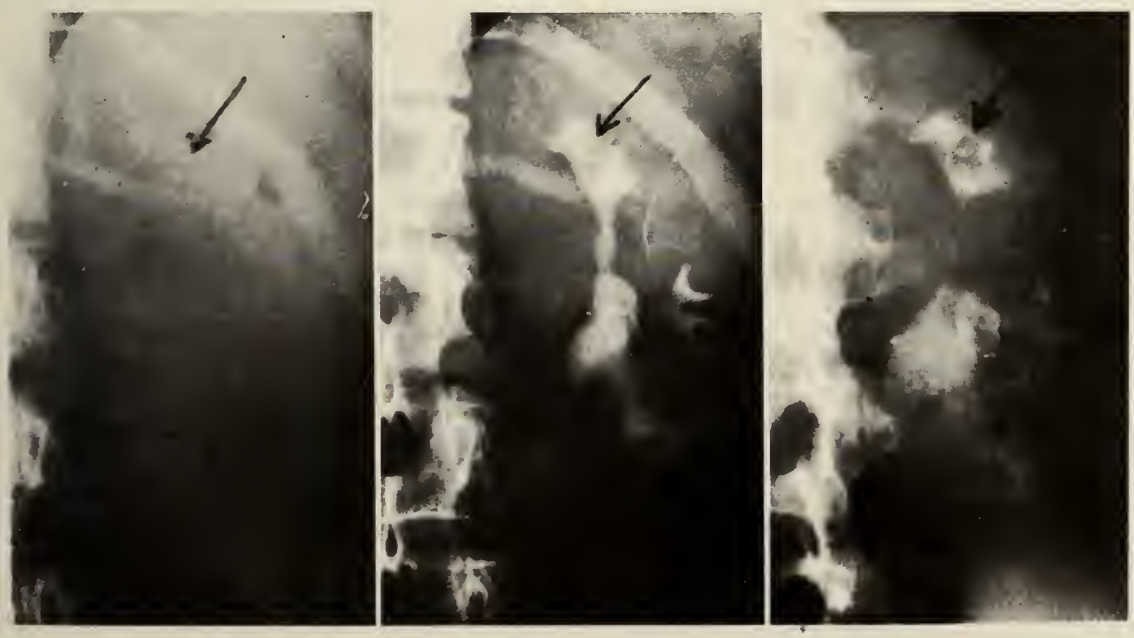

Figure 5.—Pyelgrams of a patient's kidney. Arrows show minute calcification in or on renal papilla; film with oblique projection on right. (From Vermeulen et al[18]; reproduced by permission from Journal of Urology.)

TABLE 1.—*Diagnostic Classification of 230* Consecutive Patients with Renal Stones†*

Diagnosis	*Patients*
Uric acid stones	9
Renal tubular acidosis	9
Medullary sponge kidney	16
Primary hyperparathyroidism	10
Sarcoidosis	4
Hyperthyroidism	2
Vitamin D or calcium excess	2
Inflammatory bowel disease	9
Chronic diarrheal states	7
Jejunoileal shunts	2
Infection	8
Cystinuria	3
Alkali abuse	2
Acetazolamide administration	1
Idiopathic calcium stones‡	146
TOTAL	230

*Only 84 (37 percent) of the 230 patients had well-established disease.

†Data from Coe and Kavalach.[20]

‡In 14 patients there were some stones composed of uric acid mixed with calcium oxalate; however, calcium oxalate stones were the predominant stones formed.

sis (for example, strong family history, gouty trait, hypercalcemia, chronic malabsorptive small bowel disease, fasting or severe reducing diets).

Once a physician has made a diagnosis of nephrolithiasis, he should try to determine why the stone developed and what can be done to prevent new stone formation. A knowledge of the relative frequency of the various causes is of basic importance. Table 1 lists the diagnostic classification of 230 *consecutive* patients with renal stones[20]; it is similar to the experience in most clinics. More than 50 percent of patients have idiopathic calcium stones; about 40 percent of patients with calcium stones have idiopathic hypercalciuria.

In this clinical conference, the major causes of stone formation listed in Coe's diagnostic classification (Table 1) will be presented. We hope to end this conference on a note of optimism regarding our understanding of pathogenic mechanisms, diagnosis, treatment and, most important, prevention.

Dr. Coburn will discuss patients in whom calcium oxalate stones (one of the most common types of kidney stone) form. Although he will focus primarily on patients who do not have hypercalciuria or hyperparathyroidism, the physiochemical mechanisms of stone formation that he will discuss may apply to patients with these diagnoses as well.

Calcium Oxalate Stones—Pathogenesis, Clinical Problems and Treatment

JACK W. COBURN, MD*

MANY PATIENTS with renal calculi that contain calcium have idiopathic hypercalciuria or a parathyroid adenoma; however, in 40 percent to 50 percent of those with typical calcium oxalate stones, urinary calcium excretion may be within a defined "normal range."[21,22] An excess concentration of the constituent solutes, calcium and oxalate, may contribute to the pathogenesis of stones. Calcium stones occur with increased frequency in patients whose primary problem is hyperuricosuria or cystinuria. Deficiency of a naturally occurring inhibitor of precipitation may likely contribute to the pathogenesis of stones, particularly because normal urine is commonly supersaturated with oxalate.

During the past several years, Robertson, Peacock and Nordin,[9] from Leeds, and Pak,[23] from Dallas, have evaluated the role of the saturation of urine with either calcium oxalate or brushite (calcium phosphate) as factors contributing to the pathogenesis of stones. The English workers calculated the saturation products from the various ionic strengths, the urinary pH and the formation constants for various calcium complexes.[9] Pak[23] evaluated the growth or regression of synthetic crystals of calcium oxalate or brushite in urine. With these methods, urine can be characterized as containing oxalate at levels above the solubility product, at which point urine is supersaturated and crystal growth (but not new formation) can occur. At higher solute concentrations, the formation product (a point of supersaturation from which precipitation of new crystal may occur) is reached.

When the formation product for calcium oxalate was evaluated in urine specimens from normal subjects and from those in whom recurrent renal stone formation occurred, there were statistical differences between the means of the two groups; however, considerable overlap existed for individual subjects.[11] Values for most urine specimens from normal subjects were either supersaturated or exceeded the formation product. In the same urine specimens, Robertson and asso-

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ciates[11] tested for the presence of inhibitory substances by measuring the growth of seed crystals of calcium oxalate in a standard supersaturated solution with and without addition of a small volume of test urine; thus, the degree of retardation of crystal growth was quantitated. Urine from patients with recurrent stone formation was found to inhibit less growth than urine from normal subjects. Nevertheless, considerable overlap existed between the two groups. When the effects of both the activity product and inhibitory capacity were evaluated, a distinct difference was noted between the urine specimens from patients in whom stones recurred and those from normal subjects. They calculated a "line" that best separated the two groups and estimated the combined contribution of a formation product and the extent of inhibitory factors as the distance from the line, a characteristic termed the saturation-inhibitor index. This index provided good separation between the values of the urine specimens from patients with renal stones and those from normal subjects. Such observations suggest that urinary concentrations of calcium and oxalate, and reduced presence of unidentified inhibitors of calcification, contribute toward the pathogenesis of stones.

Certain inhibitors of crystal formation may exist in urine, including pyrophosphate, magnesium, various amino acids, certain trace elements and some values of urine pH. Of these, pyrophosphate is a highly potent natural inhibitor of crystal formation; however, the concentrations of pyrophosphate are not reduced in the urine of those in whom renal stones are formed. Thomas and Howard[24] characterized urine as being "good" or "evil" based on its capability to inhibit the calcification of rachitic rat cartilage. It has recently been suggested that phosphocitrate may be responsible for inhibition of calcification.[12] Nevertheless, it has not been possible to classify or identify patients with idiopathic renal stone formation on the basis of the presence or absence of a specific inhibitor in their urine.

Diphosphonates may be used potentially as therapeutic agents in stone disease; they are chemically synthesized analogs of pyrophosphate, which are not subject to degradation by naturally occurring pyrophosphatases.[25] In solutions of synthetic urine, the diphosphonates are highly effective in preventing crystal growth.[25] However, the amount of diphosphonates required to prevent urinary stone formation may lead to abnormal skeletal mineralization.[26,27] The future clinical application of these compounds remains uncertain.

Of all the constituents present in urine, oxalate is one that is most likely to induce serious and recurrent nephrolithiasis, especially when its concentration is increased. There is disagreement about the role of augmented oxalate in contributing to stone formation, except under unusual circumstances. The amount of urinary oxalate has been found to be normal in most patients with renal stones.[28] However, others have noted that many persons in whom idiopathic stone formation occurs may show periodic increases in urinary oxalate.[29,30] Oxalate is produced as an end product of glycine metabolism, which cannot be metabolized; it arises from glyoxylate or glycolate. Increased oxalate excretion in the urine can occur because of increased generation of its precursors or because of inhibition of the pathways whereby glyoxylate or glycolate are converted to compounds other than oxalate.

Two forms of primary hyperoxaluria exist; they are usually manifested by recurrent stone formation with progressive renal failure in childhood or adolescence.[31] Acquired hyperoxaluria occurs most commonly as a consequence of disease of the small intestine; it is present in 7 percent to 30 percent of patients after resection of the ileum or an intestinal bypass operation for extreme obesity.[32,33] Although the mechanism is not certain, hyperoxaluria is believed to occur because of extensive absorption of oxalate. It has been postulated that calcium is poorly absorbed because of the formation of calcium soaps in the intestinal lumen. Normally, calcium present in the intestinal lumen precipitates as insoluble calcium oxalate, which is nonabsorbable. With the binding of calcium to soaps, a larger fraction of oxalate is free and can thus be absorbed.

The addition of oxalate to the diet of patients with hyperoxaluria substantially augments urinary oxalate compared with a small increment in oxalate that occurs after the same addition of oxalate to the diet of normal persons.[34] The management of these patients should include a reduction of the dietary intake of oxalate. Foods that are high in oxalate content, such as spinach, mustard greens, Swiss chard, other leafy green vegetables, rhubarb and tea, should be avoided. The administration of cholestyramine, which may modify bile salts and render oxalate nonabsorbable, may also reduce urinary oxalate excretion

under certain conditions. Earnest, Williams and Admirand[35] have reported that the administration of calcium salts can lead to a substantial fall in urinary oxalate excretion. Recurrent renal calculi and renal failure caused by oxalosis are serious complications of intestinal bypass operations and the "vanishing bowel" syndrome associated with ileal disease; such patients should have periodic assessment of urine oxalate and renal stone formation to avoid serious and irreversible complications.

Many patients with recurrent calcium oxalate stones have increased amounts of uric acid in plasma and urine; however, the stones may contain no uric acid. Recently, Coe and colleagues,[36] and Pak and Arnold[37] found that the addition of sodium urate (but not uric acid) to artificial solutions containing calcium and oxalate enhanced the precipitation of calcium oxalate. This finding provides a basis for the empiric observation that the administration of allopurinol is effective in reducing the prevalence of nephrolithiasis in patients with hyperuricosuria and calcium oxalate stones.

With this background, available means for managing patients with urolithiasis caused by calcium oxalate can be reviewed. Two of the major principles of management are reduction in dietary calcium uptake and intake of copious quantities of fluid. Indeed, compliance to such a regimen may explain why several workers have noted that the prevalence of stones decreases in patients who are followed regularly in a clinic that specializes in kidney stones[20] and by physicians who are interested in urolithiasis. Cellulose phosphate, which decreases intestinal calcium absorption by binding calcium in the intestine and rendering it nonabsorbable,[38] can substitute in part for reduced calcium intake. Although reduced intestinal absorption may contribute to osteoporosis or secondary hyperparathyroidism, there are no data indicating that this risk is great.[39] Urinary oxalate levels increase during treatment with cellulose phosphate.[40] This agent remains an investigational drug in the United States, although it has been used in the United Kingdom.

The thiazide-type diuretics make up a group of drugs that reduce urinary calcium excretion and thereby reduce the incidence of stones.[41] These agents reduce urinary calcium excretion due, in large part, to a contraction of extracellular volume, which augments more proximal tubular reabsorption of sodium, calcium and other solutes.[42] In the distal nephron, these diuretics inhibit distal tubular calcium reabsorption to a very small extent compared with a major effect on sodium reabsorption.[43] These agents can reduce the urinary calcium excretion in normal persons as well as in patients with hyperparathyroidism and idiopathic hypercalciuria. To achieve a desired effect, dietary sodium intake should be moderately decreased, that is, below 7 to 10 grams (100 to 150 mEq) of sodium per day.

Edwards and associates[44] have reported the successful management of urolithiasis by ingestion of neutral salts of orthophosphate. However, other investigators, using a slightly lower dose, found no benefit in a double-blind controlled study.[45] The mechanism whereby orthophosphate can reduce the occurrence of stones is not entirely clear. Usually, there is a decrease in urinary calcium excretion, and pyrophosphate excretion may increase; the latter could reduce stone formation by acting as an inhibitor of crystal formation. Finally, the oral administration of magnesium, which may act as an inhibitor of calcification, may be considered an adjunct in the management of certain patients with renal stones disease.[46]

At present, it is possible to reduce greatly the incidence of stones or to prevent their recurrence with use of these therapeutic modalities. Therefore, empiric therapy, which is aimed at reducing the quantities of calcium (or oxalate) in the urine, or the addition of an inhibitor may be effective in managing recurrent nephrolithiasis, despite a lack of knowledge of the pathogenesis of renal stone disease.

DR. KLEEMAN: *Studies in outstanding "stone" clinics show that nearly all patients in whom idiopathic stones are formed have hypercalciuria; and, within this group, there are a few cases of primary hyperparathyroidism. Doctor Brickman will report on the causes of hypercalciuria in these patients.*

Idiopathic Hypercalciuria in Patients with Kidney Stones

ARNOLD S. BRICKMAN, MD*

MANY PERSONS with calcium-containing kidney stones seem to excrete excessive amounts of calcium in the urine. Although few patients may

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show signs of clinically overt primary hyperparathyroidism, most of them fit into a loosely characterized group, originally designated by Albright and associates[47] as having idiopathic hypercalciuria. At present, the favored view is that hypercalciuria is a common expression of perhaps several distinctive metabolic disorders affecting primarily the intestine or the kidney.

There are three predominant theories about the pathogenesis of hypercalciuria: (1) the primary intestinal defect hypothesis (absorptive hypercalciuria), (2) the "renal calcium leak" hypothesis (renal hypercalciuria) and (3) the "renal phosphorus leak" hypothesis.

Intestinal Defect Theory

Intestinal hyperabsorption of calcium has been documented as a frequent finding in patients with kidney stones and with hypercalciuria.[48-51] However, the occurrence of augmented calcium absorption, although possibly a primary phenomenon, is predicted in both the renal calcium and phosphorus leak hypotheses as a secondary event. In both of these theories, intestinal absorption of calcium occurs as a consequence of enhanced conversion of 25-hydroxycholecalciferol (25-OH-D_3) to 1,25-dihydroxycholecalciferol (1,25-$[OH]_2D_3$) either by the stimulus of hyperparathyroidism or by a lowered level of serum phosphorus.[52-54] Thus, the presence of enhanced intestinal absorption of calcium alone cannot be used to distinguish the pathogenesis of hypercalciuria. In patients with a hypothetical primary disorder of intestinal calcium transport, hypercalciuria occurs as a consequence of an augmented filtered load of calcium to the kidney and the secondary suppression of parathyroid hormone action. The latter results from the slightly raised levels of serum calcium attributable to increased intestinal absorption. Another feature, which has been used to characterize patients with primary absorptive hypercalciuria, is a normal urinary calcium:creatinine ratio after a 12-hour to 14-hour fast.[55] Bordier and co-workers[56] have also suggested that when diets low in calcium content are ingested, patients with absorptive hypercalciuria may have lower levels of urinary calcium excretion than those with renal calcium or phosphorus wasting; however, relative hypercalciuria is present in all three groups. Therefore, evidence for primary absorptive hypercalciuria[55,56] includes augmented intestinal absorption of calcium, normal levels in serum of calcium and phosphorus, normal to low levels of parathyroid hormone, normal urinary excretion of cyclic adenosine-3′,5-monophosphate (AMP), and a normal fasting urinary calcium: creatinine ratio.

The nature of the hypothetical intestinal defect is not known. Kaplan and colleagues[57] have reported elevated levels of circulating 1,25-$(OH)_2D_3$ in some patients with apparent absorptive hypercalciuria as characterized by the above criteria. Thus, overproduction of this sterol could explain enhanced intestinal absorption; however, it seems to exclude the intestine as the site of the primary defect. A second explanation could be altered intestinal sensitivity to 1,25-$(OH)_2D_3$. This hypothesis could explain the finding of normal levels of 1,25-$(OH)_2D_3$ in some patients with absorptive hypercalciuria.[57,58] Finally, the enhanced intestinal absorption of calcium may not be vitamin D-mediated.

Renal Calcium Leak Theory

Several investigators have suggested the presence of decreased renal reabsorption of calcium as an explanation for hypercalciuria in patients in whom stones form. In early studies, Edwards and Hodgkinson[59] reported an elevated clearance of calcium in 14 patients with hypercalciuria. They also found that an elevated urinary calcium:creatinine ratio occurred in some fasting patients in whom stones occurred, and interpreted this as indicating a renal wasting of calcium. Pak and associates[55] found this defect in 2 of 30 patients, whereas Coe and colleagues[60] and Bordier and colleagues[56] (both groups of investigators relying mainly on the findings of normocalcemic hyperparathyroidism) found a renal calcium leak in 26 of 40, and in 22 of 71 patients, respectively. Coe and associates[60] have suggested that the renal calcium leak hypothesis could be tested by examining the effect of suppression of hypercalciuria on the elevated levels of parathyroid hormone. They reported that the reduction of urinary excretion of calcium by hydrochlorothiazide therapy resulted in suppression of hyperparathyroidism in patients with stones and mild hypercalciuria. In contrast, administration of furosemide to normal volunteers resulted in a calciuric response associated with a rise in parathyroid hormone. Other workers have found thiazide-induced suppression of intestinal absorption of calcium in these patients.[61,62] At present, additional evidence supporting defective renal tubular handling of filtered calcium is lacking.

The nature of the putative defect in renal calcium handling is unknown. Lemann, Piering and Lennon[63] found exaggerated calciuric and magnesuric responses to oral or intravenous administration of glucose loads after overnight fasting in patients in whom stones occurred. However, these investigators did not attempt to subclassify their patients according to possible pathogenesis of hypercalciuria.

Renal Phosphorus Leak Theory

Of the three theories discussed, this is the most recent, having evolved mainly as a consequence of continuing advances in our understanding of vitamin D metabolism. The tendency toward low levels of serum phosphorus or frank hypophosphatemia has been recognized as a frequent finding in patients with hypercalciuria.[47,64,65] Several workers have emphasized the finding of slightly enhanced fractional excretion of phosporus or a decreased threshold for phosphorus excretion (tubular maximum for phosphorus transport/glomerular filtration rate [TmP/GFR]).[56,66] Llach and co-workers[67] also described augmented renal clearance of phosphorus during acute phosphorus loading in a few patients. According to the renal phosphorus leak theory, hypophosphatemia, occurring as a consequence of renal loss, stimulates production of 1,25-$(OH)_2D_3$, resulting in augmented intestinal absorption of calcium. Hypercalciuria results from the enhanced filtered load of calcium and mild suppression of parathyroid hormone. In this theory the development of hypercalciuria is analogous to that found in states of phosphorus depletion in humans. Dominguez, Gray and Lemann[68] have shown increased metabolism of 25-$(OH)D_3$ to 1,25-$(OH)_2D_3$ in experimental phosphorus depletion in humans. Gray and associates[69] have also reported an inverse relationship between the decrease in serum phosphorus and increase in plasma levels of 1,25-$(OH)_2D_3$ during phosphorus depletion.

If each of these theories of pathogenesis—intestinal defect theory, renal calcium leak theory and renal phosphorus leak—proves to be correct, and if the population of patients with so-called idiopathic hypercalciuria is made up only of patients with these disorders, then considerable overlap in their biochemical features exists. Thus, augmented intestinal absorption of calcium would be predicted for each type of patient; normal to suppressed circulating levels of parathyroid hormone would be predicted for patients with both absorptive hypercalciuria and with a primary renal phosphorus leak. Elevated levels of parathyroid hormone have been reported in patients with a proposed renal calcium leak, but they also occur in patients with so-called normocalcemic primary hyperparathyroidism.[70] In this brief review we shall not consider the latter disorder. However, the close similarity between this entity and the features described in patients with renal hypercalciuria has suggested to some investigators a causal relationship between chronic secondary hyperparathyroidism and the development of autonomous parathyroid function due to hyperplasia or the development of a tumor. Thus, the careful and systematic investigation of mineral homeostasis in stone-forming patients, together with standardization of definitions of hypercalciuria and measurements of parathyroid hormone and vitamin D analogs, is helping the categorization of patients; this should provide insights into pathogenetic mechanisms.

Dr. Kleeman: *Although patients with uric acid calculi constitute only a small proportion of the total population of those in whom stones form, they represent a group in whom good medical therapy has proved most successful. It is therapy based on sound physiologic principles. Dr. David Lee will bring us up to date on patients with uric acid stone formation.*

Uric Acid Calculi

DAVID B. N. LEE, MD*

The oldest renal stone in present-day collections contains a uric acid nucleus. It was recovered from the mummy of an Egyptian who had died more than 7,000 years ago.[71] Uric acid causes about 10 percent of all stones that are found in patients in United States.[72] The prevalence of uric acid lithiasis varies with racial background and geographic location. The highest incidence has been recorded in Israel, where in one large series of patients with urinary calculi, 39.5 percent had uric acid stones.[73] Lange[74] has traced the phenomenon of increased incidence of kidney stone formation in Germany since 1945; the frequency of patients with uric acid stones in various German clinics rose from 4.1 percent in 1958 to

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23 percent in 1965, with one clinic reaching an all-time high of 40 percent.

The formation of uric acid stones is attributed primarily to precipitation of uric acid from oversaturated urine. The degree of oversaturation and, therefore, the tendency towards uric acid precipitation is not only determined by the volume of urine and the amount of uric acid excreted, but is also critically dependent on the urinary pH. Although uric acid is almost insoluble in water, in a buffer solution (such as urine) its solubility increases as the pH rises, a result of its dissociation into urate ions.[72,75] Uric acid lithiasis either may occur in the absence of hyperuricosuria (by reduction in urine volume or urine pH or both) or may not occur in hyperuricosuria (by increasing urine volume or urine pH or both). These considerations are of fundamental importance in the clinical approach to problems related to uric acid calculus disease. Sperling and de Vries,[76] together with Kedem[77] explored the possibility that patients with uric acid lithiasis may form qualitatively abnormal urine that lacks the supersaturation-maintaining capacity for uric acid; however, their findings did not support the concept.

TABLE 2.—*Clinical Classification of Uric Acid Nephrolithiasis*

Uric acid nephrolithiasis not associated with hyperuricemia or hyperuricosuria.

- Idiopathic
  - Sporadic[72,75]
  - Familial[73,78]
- Excessive dehydration
  - Loss through skin[73]
  - Loss through intestine[81-84]

Uric acid nephrolithiasis associated with hyperuricemia with or without hyperuricosuria.

- Gout[73,75,76]
- Myeloproliferative, neoplastic, hemolytic disorders[87-92]
- Enzyme abnormalities
  - Hypoxanthine-guanine phosphoribosyltransferase (HGPRTase) deficiency: Complete (Lesch-Nyhan syndrome)[95] and partial (? variety of primary gout)[96]
  - Glucose-6-phosphatase deficiency (type 1 glycogen storage disease)[97]
  - Glutathione reductase variant[98]
  - Phosphoribosylpyrophosphate amidotransferase variant[99]
  - Mutants of phosphoribosylpyrophosphate (PRPP) synthetase[100]

Uric acid nephrolithiasis associated with hyperuricosuria without hyperuricemia.

- Excessive protein and purine ingestion[72]
- Defect in tubular reabsorption of uric acid
  - Uricosuric drugs[72]
  - Congenital or acquired defects[72,104,105]

Table 2 is adapted from published information[72,75] and represents an attempt to classify uric acid lithiasis encountered in clinical practice into broad categories. For this purpose, hyperuricemia is defined as a serum uric acid concentration of more than 6.5 mg per dl in men and 5.5 mg per dl in women; hyperuricosuria is defined as a urinary uric acid excretion of more than 800 mg per day on an average unrestricted diet.[72] The definitions of these values are arbitrary. This classification will undoubtedly undergo repeated modifications and is intended only to be used as a convenient reference framework.

Most patients with uric acid stones have neither hyperuricemia nor hyperuricosuria and fall under the diagnostic category of idiopathic uric acid lithiasis. This abnormality may occur sporadically or may be transmitted in an autosomal dominant pattern.[73,78] The proportion of women in this group (27.5 percent) is much higher than that found in persons with gout in whom uric acid kidney stones form (8.6 percent).[72] Henneman, Wallach and Dempsey[79] reported, however, that this disorder affected both sexes with equal frequency. The only physiologic deviation present in these patients is a persistently low urinary pH, which remains fairly constant (below 5.4) with little variation through the day. The normal late-morning and postprandial "alkaline tides" (marked by a rise in urinary pH to more than 6.0) are absent in these patients. This inability to increase urinary pH is considered important in the precipitation of uric acid in the urinary tract, even though the quantity of uric acid excreted is not excessive. Decreased ammonia formation has been proposed by some investigators,[72,79] and refuted by others[75,80] to be important in the development and maintenance of urine with an inappropriately low pH.

Increased prevalence of uric acid stones in persons working in arid and parched areas has been attributed to severe reduction in urine volume. Atsmon, de Vries and Frank[73] pointed out that in desert regions a fluid intake of 10 to 15 liters may be necessary to maintain a daily urine volume of one liter.[77] Uric acid stones are also seen in patients with ulcerative colitis, re-

gional enteritis and ileostomies.[81-84] Low urine volume, increased uric acid excretion and systemic metabolic acidosis with excessively acidic urine[83,84] have all been considered important in the development of uric acid stones in these diarrheal states.

Uric acid stones may develop in patients with hyperuricemia with or without concomitant hyperuricosuria. In about 20 percent of patients with primary gout in the United States uric acid lithiasis occurs[72]; in Israel, the incidence of uric acid stones in persons with gout is as high as 75 percent.[73] The difference may be attributed to several factors including variations in racial background, climate and geographic location. In addition, the diagnostic criteria for primary gout are also not uniform.[75] Both hyperuricosuria and acidic urine have been considered important predisposing factors in uric acid stone formation in patients with gout. However, most patients (70 percent) with gout do not excrete excessive uric acid in the urine.[72] Also, in patients with gout, only 47 percent of those in whom stones form and as many as 28 percent of those in whom stones do not form, have persistently acidic urine.[85] Nephrolithiasis may precede the first development of acute arthritis, in some cases by more than a decade.[72,86]

Hyperuricemia and hyperuricosuria may result from an increase in cellular nucleic acid metabolism by excessive production or destruction of cells. Clinical examples include polycythemia vera, myeloid splenomegaly, myeloid leukemia, myelomas and sickle cell anemia.[87-92] Vigorous cytolytic therapy in these conditions may lead to fulminant hyperuricemia (more than 50 mg per dl has been documented in patients with leukemia). Pronounced hyperuricemia may result in the development of acute renal failure[93] attributed to precipitation of uric acid and urate in both the collecting ducts and the renal vascular complex.[94]

Several enzyme abnormalities have been documented in patients with hyperuricemia,[95-102] in whom there is a high occurrence of uric acid lithiasis. Hyperuricosuria[101] and low urine volume[102] are considered important factors in the causation of stone formation in these patients.

The last group of patients with uric acid lithiasis is characterized by hyperuricosuria without overt hyperuricemia. Excessive consumption of protein and purine is an often quoted example. The surplus uric acid formed is rapidly cleared by the kidneys causing no perceptible changes in serum uric acid concentration.[72] Use of uricosuric agents is another cause of increased urinary uric acid. In 16 percent of patients with gout in whom uric acid lithiasis developed, stone formation was attributable to the liberal intake of uricosuric agents.[72]

An inborn defect in renal tubular handling of uric acid and hyperuricosuria is believed to be the cause for the high prevalence of uric acid lithiasis seen in the dalmatian coachhound.[103] A similar inborn defect in renal tubular handling of uric acid has been shown in humans.[104,105] Increased uric acid excretion may also occur as part of a generalized defect in tubular function—the renal Fanconi syndrome. The absence of uric acid lithiasis in these conditions may be due to the concomitant bicarbonate wastage and the development of renal tubular acidosis.[72] The interrelationship between hyperuricosuria and recurrent idiopathic calcium nephrolithiasis is discussed by Dr. Narins in this symposium.

Clinical Features

Patients with uric acid lithiasis usually complain of passage of reddish sand, gravel or stone. The history may include recurrent colic, urinary obstruction and infection. A history of gout in the patient or in the family members, or both, is present in some cases. Persistently low pH and the presence of uric acid crystals in repeated analysis of urine are helpful diagnostic findings. Hyperuricemia or hyperuricosuria, or both, may be present, although in many patients with uric acid lithiasis both features may be absent. Findings on intravenous pyelography show a radiolucent shadow or shadows. The differential diagnosis for exclusion includes cystine stone and tumor.[72,75]

Treatment

The development of rational and effective treatment for uric acid stones has virtually eliminated the necessity for surgical operations in these patients. Effective treatment consists of (1) decreasing urinary uric acid concentration by increasing urine volume (high fluid intake) and decreasing uric acid production and excretion (allopurinol administration); and (2) increasing uric acid solubility by increasing urine pH (alkalinizing medications). If the patient is not ingesting excessive amounts of purine and protein (for

example, no more than 90 grams per day), dietary restrictions may be dispensed with.[72]

In more than 80 percent of patients with uric acid nephrolithiasis, increased fluid intake and alkalinization constitute sufficient therapy for control of further recurrences.[72,75] In some patients, partial and complete dissolution of existing stones was also observed. Fluid intake should be adequate to sustain a urine volume of least 1.5 to 2 liters per day. Therapy with sodium and potassium salts given orally is usually carried out to achieve a urine pH of 6.0 to 6.5. Insofar as is practicable, the urine flow and pH should be maintained as evenly as possible around the clock. Spot checks of urine pH with nitrazine paper may be done by the patient at home.

In patients who are either refractory to the above therapy or unsuitable for liberal hydration and alkalinization (for example, patients with precarious cardiovascular status), 200 to 400 mg of allopurinol per day may be administered in divided doses.[72] Allopurinol is rapidly oxidized to oxipurinol, which is also an effective xanthine oxidase inhibitor.[106] In contrast to the short half-life of allopurinol in plasma (1 to 1½ hours), that of oxipurinol is extremely long (18 to 30 hours). Some clinicians, therefore, prefer to give allopurinol in a single daily dose.[107] In patients with impaired renal function, a dosage of 100 mg of allopurinol per day may be adequate to maintain xanthine oxidase inhibition, because the clearance of oxipurinol is proportionately reduced. In a study of 108 patients refractory to conventional therapy, recurrence of renal colic and passage of uric acid stones discontinued in all except 10 patients soon after the institution of allopurinol therapy.[72]

Side effects of allopurinol include skin rash, drug fever, gastrointestinal irritation, thrombocytopena, impotence and granulocytopenia.[72,75] Skin rash resolves rapidly after withdrawal of allopurinol. Reinstitution of therapy in some of these patients was not followed by recurrence of the rash. With rare exceptions,[108,109] allopurinol administration did not cause overt problems with xanthine crystalluria and stones.[110] The inhibition of xanthine oxidase will retard the degradation of azathioprine and 6-mercaptopurine. In patients receiving these medications, the use of allopurinol should be avoided when possible. Otherwise, the dosage should be substantially reduced and toxicity from excessive immunosuppression closely monitored.

DR. KLEEMAN: *Acquired and congenital defects in the tubular reabsorption of various urinary solutes and the excretion of hydrogen ions result in a medullary intraluminal environment conducive to the precipitation and crystallization of various solutes. These, in turn, may lead to tubular degeneration and necrosis and, very frequently, nephrolithiasis. Dr. Robert Narins will report on these unusual patients.*

Renal Tubular Disorders Causing Nephrolithiasis

ROBERT G. NARINS, MD*

THREE IMPORTANT DETERMINANTS of renal stone formation include (1) 24-hour urinary excretion of crystalloid, (2) its urinary concentration and (3) its solubility in the urine. These factors will be used as a framework for discussing the pathogenesis and therapy of nephrolithiasis in three renal tubular disorders: renal tubular acidosis, cystinuria and medullary sponge kidney.

Renal Tubular Acidosis

This syndrome may be subdivided into two major types whose pathogenesis and clinical expression differ substantially.[111] In proximal (type 2) renal tubular acidosis, bicarbonaturia occurs subsequent to the impairment of bicarbonate reabsorption by the proximal nephron. The defect in distal renal tubular acidosis (type 1) lies in the inability of the distal nephron to generate or sustain a urine of maximal acidity, despite severe systemic acidosis. In type 1, the daily load of endogenously produced acid is not excreted and a progressive systemic acidosis ensues. Unlike patients with distal renal tubular acidosis, who remain in positive acid balance, those with the proximal lesion are able to return to zero balance. The acidosis caused by their bicarbonaturia eventually lowers the filtered load of bicarbonate to an amount that can be again almost completely reclaimed by the damaged proximal nephron (Figure 6). At this point, bicarbonaturia will cease, and the urine may be again appropriately acidified and the daily load of fixed acid excreted. Thus, an inappropriately alkaline urine and positive hydrogen ion (H^+) balance characterize distal renal tubular acidosis, whereas patients with the proximal form excrete an acid urine and remain

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in zero H^+ balance, albeit at the expense of a lower serum bicarbonate concentration.

Nephrocalcinosis and nephrolithiasis frequently complicate distal renal tubular acidosis but rarely, if ever, occur in the proximal form. The prime determinant of calcium stone formation in distal renal tubular acidosis is a daily retention of acid. This results in hypercalciuria and leads to impairment of calcium's urinary solubility. The differences in calcium metabolism between types 1 and 2 of renal tubular acidosis, and the mechanisms of the hypercalciuria and calcium precipitation in the distal form of the disorder are discussed below.

The retained acid is partially buffered by bone calcium carbonate[112] causing release of calcium for excretion in the urine. The results of recent studies by Coe and Firpo[113] have shown that increased levels of circulating parathyroid hormone occur in distal renal tubular acidosis (type 1), thereby further enhancing the release of bone calcium. Consequently, bone density is frequently diminished in distal renal tubular acidosis (Table 3).

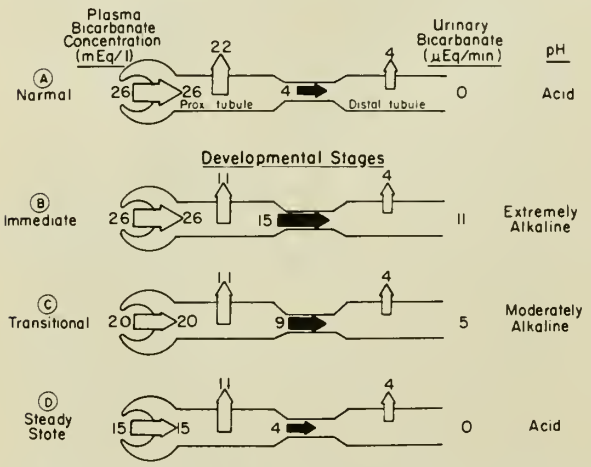


Figure 6.—Developmental stages of proximal renal tubular acidosis. Glomerular filtration, and proximal and distal reabsorption of bicarbonate designated by clear arrows. Dark arrow indicates the magnitude of the distal delivery of bicarbonate (see text for details). (Reproduced by permission from Narins and Goldberg[111]; copyright, 1977, by Year Book Medical Publishers, Inc., Chicago.)

TABLE 3.—*Pathogenesis of Nephrocalcinosis and Lithiasis in Distal Renal Tubular (Type 1) Acidosis*

Factors Causing Hypercalciuria	*Factors Enhancing Precipitation*
Bone	.....
Bone buffering	
Parathyroid hormone	
Blood	.....
Less protein binding	
Renal	Renal
Less tubular reabsorption of calcium	Alkaline urine
	Low urine citrate

An increased concentration of circulating H^+ ions will reduce the negative charge on serum proteins. Thus, as more calcium circulates in the free form, more is available for glomerular filtration. The hypercalciuria that accompanies distal renal tubular acidosis is caused not only by this increased load of calcium, but also represents an acidosis-induced inhibition of tubular calcium reabsorption.[114] The mechanism by which acidosis depresses reabsorption is unknown at present, although it is probably due to an adaptation of the distal nephron to the acidosis.[115]

Bone disease rarely develops in patients with proximal renal tubular acidosis in the absence of phosphaturia, and, despite similar degrees of systemic acidosis, hypercalciuria is usually absent.[116] This is consistent with the minimal calciuric response of normal persons to acetazolamide-induced proximal bicarbonate wasting.[115] The absence of positive H^+ balance probably accounts for the lack of bone resorption and hypercalciuria in proximal renal tubular acidosis.

The persistently alkaline urine and hypocitraturia seen in distal renal tubular acidosis predispose to calcium crystallization. The hypocitraturia seems to be a reversible function of systemic and intracellular acidosis. Acidosis stimulates both citrate reabsorption and its metabolism by the

TABLE 4.—*Therapy for Cystinuria*

Goal	*Procedure*
To enhance solubility	Alkalinization of urine (pH>7.5)
To reduce urinary cystine concentration	Water therapy of 3-4 liters per day
To reduce daily cystine excretion	A low protein diet and administration of penicillamine

TABLE 5.—*Comparison of Renal Cystic Diseases*

	Diseases		
Feature	*MSK*	*MCD*	*PCK*
Clinical course	Benign	Fatal	Fatal
Renal stones	Common	Rare	Unusual
Hypercalciuria	Common	Common	Rare
Renal tubular acidosis ...	Occurs	Rare	Rare

MSK = medullary sponge kidney, MCD = medullary cystic disease, PCK = polycystic kidney disease

epithelial cells of the renal tubules.[117] The resulting fall in citrate excretion leaves more urinary calcium in the noncomplexed form and, therefore, more prone to precipitation. The urine pH in proximal renal tubular acidosis, on the other hand, is not persistently alkaline and, therefore, hypocitraturia does not seem to occur. An associated defect in proximal citrate transport offsets any potential stimulation due to the accompanying acidosis.

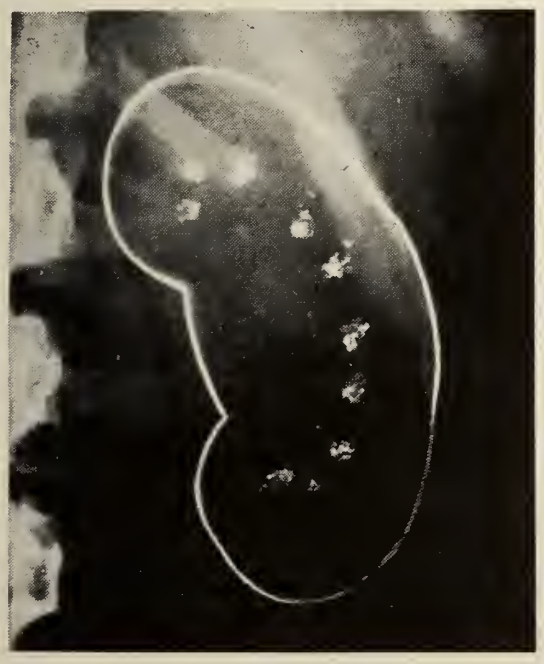
Thus, in distal renal tubular acidosis the renal delivery and excretion of calcium crystalloid is increased by its enhanced release from bone and its depressed tubular reabsorption. The high urine pH and low level of citrate excretion enhance precipitation. The absence of these features in proximal renal tubular acidosis explains the rarity of nephrocalcinosis and lithiasis in this form of the disease.

Alkali therapy reverses the effects of acidosis on bone and kidney, thereby returning the amounts of calcium and citrate excreted to within normal ranges.[118] With chronic therapy one may expect to see restoration of minerals to the bone and a diminution in preexisting nephrocalcinosis. Thus, therapy is directed toward diminishing the daily load of crystalloid and enhancing its solubility. Most patients require administration of between 80 and 100 mEq of alkali per day. This can easily be given as a mixture of sodium and potassium bicarbonate or as Shohl's solution (sodium and potassium citrate).

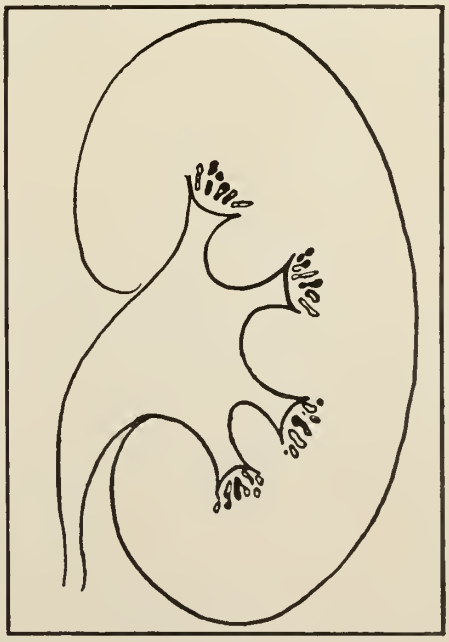
Cystinuria

The only recognized clinical expression of this disease is the urinary precipitation of the poorly soluble, sulfur-containing amino acid, cystine. This results in the formation of hexagonal (benzene-ring) crystals and eventually in radiopaque, staghorn calculi. Patients with cystinuria excrete large amounts of cystine, ornithine, arginine and lysine, despite normal plasma levels, indicating that defective tubular reabsorption and not excessive renal delivery causes the aminoaciduria. An intestinal defect in the absorption of these amino acids accompanies the renal lesion. The gastrointestinal lesion is clinically insignificant but serves as a very useful genetic marker. At present, the mechanism underlying this tubular and intestinal defect is not completely understood.[119]

The three major goals of therapy for cystinuria are outlined in Table 4. Although cystine solubility increases in alkaline urine, little benefit is



Medullary sponge kidney



MEDULLARY SPONGE KIDNEY WITH CALCIFICATION

Figure 7.—Medullary sponge kidney. Diagrammatic appearance of dilated papillary collecting ducts shown on right. Outline of the kidney on intravenous pyelogram is highlighted to emphasize the calcium stones in collecting ducts. (From Meschan[125]; reproduced by permission from WB Saunders Co.)

achieved from alkalinization until the urine pH exceeds 7.5.[120] The large dose of alkali required to achieve these pHs limits its usefulness. The intake of large quantities of water can reduce urinary cystine concentration below its saturation level of 300 mg per liter, thereby minimizing the chance of crystallization. Because many patients with cystinuria excrete 1 gram or more of cystine daily, they must drink 3 to 4 liters of water per day to achieve these low concentrations. They should awaken at night to take water and thereby prevent normal nocturnal oliguria. This is a safe and effective program that not only prevents stones from occurring but may dissolve those already present.[121] The degree of dietary protein restriction required to substantially lower cystine production and excretion is unacceptable to most patients and has little place in the routine therapy of cystinuria. Those patients who have lost substantial degrees of renal function or who have not responded to water therapy should be given penicillamine. Each molecule of cystine is composed of two molecules of cysteine, joined by a disulfide bond. Penicillamine disrupts this bond and binds cysteine, forming a mixed disulfide, which is more soluble than cystine and is excreted in the urine. With administration of 1 to 2 grams of penicillamine per day, a patient's urinary excretion of cystine can be kept below 200 mg per gram of creatinine.[122] There is a high incidence of self-limited, steroid-responsive allergic reaction to penicillamine.

Medullary Sponge Kidney

Medullary sponge kidney is one of several renal diseases in which multiple renal cysts occur. Medullary cystic disease and polycystic kidney disease are the two other major disorders. The course and clinical expression of these three diseases differ greatly (Table 5). In the infantile and adult forms of polycystic kidney disease, cysts are found throughout the kidney, leading to its progressive enlargement and destruction, eventually causing death from uremia. Hypercalciuria and stones are not usually found in polycystic kidney disease.[123] Medullary cystic disease (or juvenile nephronophthisis, as it is called in Europe) is caused by multiple cysts at the corticomedullary junction, which progressively replace renal tissue. The disease is associated with small kidneys and runs an inexorably downhill course to death in the second to third decade. These patients are often "salt-wasters," and also tend to excrete more calcium than their degree of renal failure otherwise warrants; yet nephrocalcinosis and nephrolithiasis are rare.[124]

Medullary sponge kidney is a benign disorder characterized by a variable degree of cystic dilatation of the papillary collecting ducts, which appear normal on x-ray films (Figure 7).[125] Small, discrete calcium-containing stones often develop in these dilated ducts and may serve as the first clue to the presence of sponge kidney. Because many of these patients remain asymptomatic, the diagnosis is not considered until a stone is passed, or until the renal calcifications are found serendipitously on an x-ray study of the abdomen.

Three factors may interact to cause these stones. First, the ectatic collecting ducts may lead to urinary stasis that may, in turn, predispose to calcium precipitation. Second, hypercalciuria and hypocitraturia seem to occur with increased frequency in this disorder.[126,127] Finally, in eight patients with medullary sponge kidney an associated renal tubular acidosis has been noted.[111] Four patients had overt signs of acidosis, whereas the defect could be recognized in the other four only by their failure to acidify maximally their urine in response to an acid load. The hypercalciuria in the study by Ekstrom[126] could not be related to the presence of renal tubular acidosis, but may reflect decreased collecting duct reabsorption of calcium. Thus, medullary sponge kidney is often associated with hypercalciuria, low urine citrate, inappropriately high urine pH and urine in dilated collecting ducts.

Once again, therapy is directed at lowering calcium excretion and enhancing its solubility. Those patients with associated renal tubular acidosis should be given alkali, which, in turn, may ameliorate the hypercalciuria and hypocitraturia (as mentioned previously). Chronic thiazide diuretic therapy has been used effectively to decrease the hypercalciuria seen in many patients.[127]

DR. KLEEMAN: *During past decades and up to the present, most of the fundamental laboratory and clinical investigation of renal stone disease has been done by urologists. Although efforts are being made to reduce and eliminate the need for urologic manipulation and surgical intervention, we still work very closely with our associates in urology and require their expertise and help. Dr. Richard Ehrlich of the Department of Surgery/Urology has frequently filled this role, and he will discuss the surgical aspects of renal calculi.*

Surgical Aspects of Renal Calculi

RICHARD M. EHRLICH, MD*

RENAL CALCULUS DISEASE continues to present a formidable surgical challenge. There is little, if any, disagreement about the necessity for surgical operations in symptomatic intrapelvic or calyceal calculi, which produce intermittent obstruction, infection, and hematuria or pain, or both. In these instances, the procedure is straightforward with emphasis placed on crystallographic analysis of stones, preoperative and postoperative control of infection and appropriate laboratory investigation for hyperparathyroidism.

The optimal management of the staghorn calculus, however, remains less clear. Some authors believe that nonoperative treatment is preferable in all asymptomatic patients and that renal function is not impaired by the presence of the calculus.[128] However, it has been our observation, and that of others,[129,130] that conservative treatment is complete operative removal. Swanson, Sullivan and Palmer[130] studied the cases of 30 patients with branched renal calculi in whom operative removal was carried out by various procedures. Of the patients, 83 percent were rendered free of stones and 80 percent free of infection, with no operative mortality. Furthermore, in this series renal function improved or stabilized in patients who had impairment of function before the operation.

Blandy and Singh[129] reported a 28 percent mortality among 60 patients with staghorn calculi; in 40 patients treated conservatively, pyonephrosis and other complications ensued. They concluded that all staghorn calculi should be removed, with which we agree, if preoperative evaluation of a patient's medical condition permits.

Several advances in surgical technique have made this approach valid. The parenchymal-sparing renal sinus approach of Gil-Vernet[131] and anatrophic nephrolithotomy of Smith and Boyce[132] are now used by most urologists. The latter is particularly well suited for complex, branched stones filling the entire calyceal system, and is predicated on precise vascular anatomic studies. After careful preoperative radiographic studies in multiple projections (and, occasionally, arteriography), a renal incision is made between separately supplied renal segments to spare the maximum number of nephrons. This incision is based on the anatomic fact that intrarenal arteries are "end arteries" and do not freely anastomose between segments as does the venous system. Using in vivo hypothermia (7° to 20°C) provided by iced saline slush, the ischemic period may be extended to more than two hours, which allows for enough time to insure complete stone fragment removal.[133]

The other surgical procedures, such as pyelocalycotomy[134] and lower pole partial nephrectomy,[135] are helpful in special conditions to prevent stone recurrence, but do result in some renal parenchymal loss. No one operative approach is applicable to all situations, and thorough familiarity with the above is mandatory for urologic surgeons.

Successful surgical operations to remove stones is predicated on meticulous attention to metabolic, bacteriologic and renal function evaluation, and implies complete removal of all stone fragments and correction of anatomic deformities. For an excellent in-depth analysis of the important facets of this type of procedure, we recommend the report of the Symposium on Renal Lithiasis.[136]

The ileal ureter deserves special mention. At the UCLA Hospital a total of 44 patients have been treated with ileal substitution for multiple recurrent renal calculi refractory to traditional forms of therapy. This procedure, although surgically demanding, is excellent in patients with severe nephrocalcinosis and a history of passing multiple stones. The principle of the procedure is to provide maximum drainage of the renal pelvis and lower calyces. This is to prevent recurrence of stones and to allow free passage of stones already formed into the bladder where they will be voided easily or removed cystoscopically. Contraindications to the procedure are small bowel disease, serum creatinine (higher that 2 mg per dl), neurogenic bladder or outlet obstruction.[137,138]

Most surgical failures and recurrence of stones are related to incomplete removal of fragments of the original stones. Operative nephroscopy, copious irrigation and intraoperative radiography are mandatory surgical aids to insure that even the smallest fragments are removed. If this is not successful, continued infection with urea-splitting organisms is likely. A concomitant de-

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creased solubility of both struvite and calcium salts in the resultant alkaline medium assures reformation of stones.

A recent resurgence of interest in coagulum pyelolithotomy (the formation of an intrapelvic clot with fibrinogen and thrombin) deserves special mention and has been used with outstanding success in removing small intrapelvic fragments and tiny stones. Fibrogen and thrombin are injected into the renal pelvis simultaneously, the coagulum enmeshing stone fragments. The clot is then removed with the entrapped material. Its use has not received the attention it warrants, but will probably be more widely employed in the future.[138-142]

Another indispensable aid for postoperative stone dissolution in those instances where it is impossible to free the kidney of fragments intraoperatively is the use of hemiacidrin (Renacidin, Guardian Chemical Corporation, Long Island, NY 11787)[143-145] in renal irrigation via indwelling nephrostomy. It is safe and effective but must be used with appropriate clinical safeguards, particularly the assurance of sterile urine.

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Myasthenia Secondary to Penicillamine

MYASTHENIA HAS BEEN FOUND to be a complication of penicillamine, a drug being used increasingly in the treatment of rheumatoid arthritis. . . . After years of speculation about a possible chemical abnormality as the cause of myasthenia, recent work has pinpointed the defect to a decreased number of available acetylcholine receptors in muscle. The decrease in the number of available receptors is due to the binding of many of these receptors by antiacetylcholine receptor antibodies. . . . Since penicillamine is known to produce some of its complications by means of antibody induction, and since myasthenia is now felt to be caused by antiacetylcholine receptor antibodies, which block uptake of the neural impulse at the neuromuscular junction, one can speculate that penicillamine may induce antibody to acetylcholine receptors and thereby cause myasthenia in susceptible patients. So far, more than 30 cases of penicillamine-induced myasthenia have been reported, and almost all of the cases have resolved simply by withdrawing the drug. . . . Treatment with standard antimyasthenia therapy is usually unnecessary.

—PAUL E. PATAKY, MD, *Boston*

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Amebic Liver Abscess

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

DR. SMITH:* *In this conference we will discuss amebic liver abscess, a subject prompted by the diagnosis in a patient recently seen on our medical service. We have asked Dr. Robert Goldsmith to review this entity for us.*

DR. GOLDSMITH:† Before discussing the diagnosis and management of amebic liver abscess, I wish to give a broader view of the disease. What is the prevalence of amebic liver disease in the United States today? How often is one likely to see it, and what syndromes might one encounter in association with it?

In a review of 166 surveys nearly two decades ago, Burrows estimated a prevalence rate for amebiasis in the United States of about 5 percent.[1] Because so few surveys have been conducted since then, relatively little is known about its current prevalence.[2-4] Higher rates are found in custodial institutions and under conditions of poor sanitation and crowding. Prevalence rates of 11 percent to 45 percent were reported from five mental institutions and of 2 percent to 24 percent from four Indian reservations.[4] Other groups at increased risk are immigrants, visitors and travelers from areas of the world that are highly endemic for amebiasis. The most important mode of transmission in the United States is transfer from person to person within households. Transmission by food handlers and by contaminated water is less common.[2-4] Recently, investigators have noted the frequent venereal transmission of amebiasis in homosexual men in urban areas; it is often accompanied by other enteric infections including giardiasis, hepatitis, shigellosis and nonpathogenic protozoa.[5]

Clinical Syndromes of Amebiasis

The clinical syndromes of amebiasis[6-10] are shown in Table 1. Asymptomatic and mild intestinal infections are seen more commonly; severe intestinal infection and hepatic abscess are less frequent. Ameboma and infections in other extraintestinal sites are rarely observed in patients in the United States.

Asymptomatic Infection

In practice one may diagnose an asymptomatic amebiasis infection as a result of examining the fellow household members or sexual contacts of a patient known to have amebic disease, or after examining asymptomatic persons recently returned from an endemic area abroad. Such asymptomatic cyst carriers should be treated because over the following few years symptomatic

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TABLE 1.—*Clinical Syndromes Due to Amebic Infections*

Intestinal
Asymptomatic intestinal infection
Mild intestinal infection (nondysenteric colitis)
Severe intestinal infection (dysenteric colitis)
Ameboma
Extraintestinal
Hepatic abscess
Infection of other tissues

TABLE 2.—*Pathologic Features of the Liver Caused by Amebic Infections*

Real Disease Entities
• Amebic liver abscess Enlarged, painful, tender; fever
• Nonspecific hepatomegaly Slight enlargement and tenderness associated with intestinal amebiasis
Theoretical Disease Entity
• Amebic hepatitis Pathologic characteristics have not been documented

intestinal disease or a liver abscess may develop. Also, these carriers may be a source of infection for others. However, most asymptomatic persons will probably never become symptomatic, and eventually their infections will resolve spontaneously. Nevertheless, because of the possible existence of stable, nonpathogenic strains of *Entamoeba histolytica,* controversy continues over whether to treat asymptomatic infections.[11,12] Therefore, until laboratory means are found to identify such strains, it is prudent, in countries where pathogenic strains are endemic or frequently imported, to view all *E histolytica* isolates as potentially pathogenic.

A reminder—steroids and immunosuppressive drugs can cause severe exacerbations of quiescent intestinal amebic infections. Therefore, the disease should be thoroughly ruled out before these drugs are used to treat other conditions.

Mild to Severe Intestinal Infections

In a case of mild intestinal disease, the patient has a few bowel movements a day, which are free of blood or mucus. As the severity of the intestinal infection increases, the patient may have 10 to 20 or more bowel movements a day, with increasing amounts of blood, mucus and bits of necrotic tissue and decreasing amounts of fecal matter. In severe cases, patients often experience pronounced weakness, vomiting, high fever, weight loss and diffuse abdominal tenderness; frequently, they also have low-grade hepatic enlargement and tenderness.

Ameboma

I recall a patient seen in San Francisco about eight years ago. He was a 45-year-old man who had recently returned from Mexico. A roentgenogram of the large bowel showed an annular lesion. The working diagnosis was carcinoma. He was operated on, but died several days later. The final diagnosis was not carcinoma but ameboma and amebic peritonitis. Ameboma is an unusual manifestation of intestinal amebiasis in which a granulomatous reaction to *E histolytica* results in a stricture or tumor that may project into the bowel lumen or become an annular lesion. Amebomas are found in the large bowel, most often in the cecum or rectal areas; clinically and radiologically, they may resemble bowel carcinoma or tuberculosis.

I have described this patient's illness to emphasize the need, when taking a medical history, for asking questions about travel and residence: "Where have you traveled recently?" And, "Where have you lived in past years?" The responses may help to determine whether an exotic disease should be included in the differential diagnosis. Perhaps if the patient had been asked such questions, knowledge of his exposure to amebiasis while in Mexico might have suggested ameboma as a possible cause of a constricting bowel tumor.

Hepatic Amebiasis

I wish now to focus on amebic infection in the liver.

In appraising the liver's response to amebic infection, investigators have had a continuing controversy about the types and pathogenesis of lesions[8,9,13,14]: two disease entities have been clearly established, the third remains theoretical (Table 2). The real entities are amebic liver abscess and nonspecific hepatomegaly. The latter is a low-grade enlargement and tenderness of the liver that accompanies moderate to severe intestinal infection. The enlargement is probably a toxic response to the intestinal infection and is nonspecific. It is postulated that gut infection allows bacterial toxins or products of tissue destruction to gain access to the liver. The hepatomegaly is a nonspecific response because (1) findings of liver scans and biopsies are negative, and (2) when one treats the intestinal infection with luminal-specific drugs but does not treat the liver

infection with hepatic-specific drugs, the intestinal infection is eradicated and the liver enlargement and tenderness clear as well. The most frequently promulgated theoretical entity is amebic hepatitis, which is defined as the diffuse spread of trophozoites throughout the liver, causing microscopic inflammatory lesions. However, pathologic studies have failed to provide conclusive evidence for the diffuse spread of amebas or for the theory that the disease proceeds from a presuppurative, inflammatory lesion to an abscess. This contrasts with the accepted view that amebas survive and multiply in the liver, immediately causing focal hepatic necrosis as a result of their cytolytic activity, and that subsequently the microabscess enlarges concentrically.

Cardinal Features of Amebic Liver Abscess

Amebic liver abscess, although a relatively infrequent sequel to intestinal infection, is not uncommon given the large number of intestinal infections. An abscess may occur months to years after onset of intestinal infection, and often after intestinal symptoms have disappeared. Detectable abscesses range in size from small (about 2 ml) to massive (over 5 liters). They may be single or multiple, and they occur more often in the right lobe and in males.

For most patients the disease is an acute process; however, in a few it is a chronic indolent disease. In a review of 400 consecutive admissions for amebic liver abscess in Durban, South Africa, Adams reported that 59 percent of patients had acute symptoms (referable to the liver) for less than two weeks; only 5 percent had symptoms for more than 12 weeks. Concurrent intestinal symptoms were reported by 14 percent of the patients at the time they were seen, and 19 percent reported a previous history of dysentery.[8]

The cardinal signs and symptoms of amebic liver abscess are a continuous, dull to severe pain in the hepatic area, liver enlargement, intercostal or subcostal tenderness, and fever with temperatures of 39°C (102.2°F) or higher (Table 3). Pain may be felt in the epigastrium, and when the right diaphragmatic area is involved, the pain may be pleuritic or referred to the right shoulder. Typically, the pain is increased by percussion. Enlargement of the liver may be subcostal, or there may be a localized bulging of the rib cage. It may also present as a right subdiaphragmatic process: diminished movement of the diaphragm at fluoroscopy, dullness to percussion, reduced breath sounds, rales or a rub. Systemic symptoms including chills, night sweats and malaise may be present, and the patient is often prostrate. Rarely, a large abscess compresses the biliary outflow causing obstructive jaundice.

TABLE 3.—*Cardinal Features of Amebic Liver Abscess*

Signs and Symptoms	*Frequency (Percent)*
Pain	85- 99
Generalized enlargement of liver	75- 95
Intercostal or subcostal tenderness	75- 85
Fever, 39°C (102.2°F)	80-100
Prostration	50
Signs at right base	45
Gastrointestinal symptoms	5- 25
Epigastric tenderness	20
Chills and sweating	30- 60

TABLE 4.—*Typical Laboratory Findings in Patients With Amebic Liver Abscess*

Leukocyte count: 15,000-25,000 per cu mm (25% less than 10,000; 10% more than 25,000)

Eosinophilia: none

Normocytic, normochromic anemia: 50-80%

Abnormal liver function test results:
- Generally low-grade, no distinctive pattern
- Most common abnormalities: alkaline phosphate elevation, Bromsulphalein retention, and albumin/globulin reversal with normal total protein

E histolytica in stool: 12-18%

Aspiration of abscess contents: *E histolytica* found in 15-50%

Positive serologic test results: 95%

The composite findings suggest a clinical diagnosis of liver abscess, but they do not differentiate an amebic from a pyogenic abscess or rule out an infected cyst, hydatid or necrotic tumor of the liver. Amebic and pyogenic infections can occur concurrently in an abscess, perhaps in 2 percent to 3 percent of cases.

Without prompt treatment an amebic abscess may rupture into contiguous structures, particularly the pleural, peritoneal or pericardial spaces, or the lungs. Localized adhesions and widespread hematogenous dissemination may occur. Cachexia, secondary infection, shock and death may result.

The patient under discussion here had an illness of a week's duration, with continuous right upper quadrant abdominal pain referred to his right shoulder. Findings of radiologic studies showed a 7-cm lesion in the superior part of the right lobe of the liver. The diagnosis of amebic abscess was based on a positive serologic test re-

TABLE 5.—*Typical Laboratory Findings in Patients With Amebic Intestinal Infection*

Leukocyte count: may be elevated
Eosinophilia: none
Stool examination for *E histolytica:* Probability of finding organism in infected patients after testing three specimens is 80% and after six specimens is 90%
Sigmoidoscopy: Appearance of lesions; *E histolytica* in exudate and in biopsy specimen
Serologic test results: Asymptomatic infection: less than 10% positive; Mild intestinal disease: 10-40% positive; Severe intestinal disease: up to 90% positive
In vitro culture: presence of *E histolytica*

TABLE 6.—*Enhancing Sensitivity of Stool Examination for* E histolytica

Collect specimens at two-day intervals (intervals of three to four days are preferable) in clean container free of urine and toilet water.
Preserve immediately by mixing well, one part with formalin, and one part with polyvinyl alcohol fixative.
Substances that may block detection (collection should be delayed 10 to 14 days after their use): antibiotics, mineral oil or castor oil, magnesium hydroxide or bismuth, kaolin compounds, and saline, soap, tap water or barium enemas.

sult, presence of *E histolytica* in the stool, a gallium scan of the liver compatible with an amebic lesion and a rapid response to treatment. However, the parasite was not found in the aspirate. This patient's condition could represent the occasional case of combined amebic and pyogenic infection. Pyogenic infection is suggested by the presence of many polymorphonuclear leukocytes in the aspirate and by its foul smell, a typical characteristic of pyogenic but not of amebic infections. No bacteria were cultured; however, the patient had been receiving antibiotics.

Laboratory Tests for Amebic Liver Abscess

Laboratory test results for this patient included a peripheral blood leukocyte count of only 15,000 per cu mm, which fits into the 15,000 to 25,000 range seen in about 65 percent of patients with amebic liver abscess (Table 4). Only about 10 percent of patients have leukocyte counts of over 25,000 and 25 percent have less than 10,000 per cu mm. Eosinophilia is not usually present, but most patients have a normocytic, normochromic anemia. Abnormal findings on liver function tests are frequent, but generally are low grade and of no distinctive pattern. The most common abnormalities observed are elevated levels of alkaline phosphatase in the serum, Bromsulphalein (BSP) retention and albumin-globulin reversal with normal total protein.

Additional diagnostic procedures that are useful include examination of stools for *E histolytica,* serologic testing and, for selected patients, aspiration of abscess contents to determine the causative organism. The parasite will be found in stool specimens in only about 10 percent of cases and in abscess aspirates in up to 50 percent of cases if very good techniques are used. Serologic test results will be positive for nearly all patients with the disease.

Laboratory Tests for Amebic Intestinal Infection

Although the leukocyte count may be elevated (but not to high levels), there is no eosinophilia in amebic intestinal disease (Table 5). The definitive test is detection of *E histolytica* in stool through meticulous examination. The procedure is lengthy and, therefore, costly, and unfortunately is not highly sensitive. Examination by skilled technicians of three stool specimens collected under optimal conditions from each patient known to have intestinal amebiasis will detect only about 80 percent of amebic infections. Three additional tests will raise diagnostic sensitivity to about 90 percent.[15]

For patients with amebic liver abscess, the likelihood of finding the organism in stool is only 12 percent to 18 percent. Our standard procedure is to collect three specimens at intervals of two days or longer, with one of the three specimens obtained after administration of a laxative. Intervals of three to four days are probably preferable. Specimens should be collected in a clean container without coming in contact with urine or toilet water. If the specimen cannot be brought to the laboratory within an hour, the patient should preserve it immediately by mixing one portion well with 10 percent formalin and another with polyvinyl alcohol fixative. (Polyvinyl alcohol is a poison; therefore, it should be provided in a child-proof bottle and labeled as such.) Specimen collection should be delayed 10 to 14 days if any of the substances listed in Table 6 have been taken orally because they often block detection of the organism.

Additional diagnostic tests for amebic intestinal infections include sigmoidoscopy, mucosal biopsy, serology and, when available, in vitro culture of

amebas. Although sigmoidoscopy is indicated for many patients with possible amebic liver abscess, frequently it does not contribute to the diagnosis because the intestinal phase of the disease may be minimal or have cleared. The procedure should not be preceded by a cleansing enema. In mild disease, tiny ulcers with normal surrounding mucosa may be seen. In severe disease, sigmoidoscopic findings may include edema, hyperemia, granular and friable mucosa, and large ulcers. Diagnosis depends on finding the organism in exudate obtained from the surface of the ulcers, or in exudate or liquid feces collected from the lumen. Specimens should be collected using a glass pipette (do not use a cotton swab), or by scraping the ulcer surface with a metal instrument. The material collected is used to prepare smears for direct wet examinations and for fixation in Schaudinn's solution. Some centers do mucosal biopsies routinely; the specimens are best examined by immunofluorescent methods. In vitro culture of *E histolytica* generally provides a low yield of positive results.

Radiologic and Nuclear Medicine Procedures

Routine radiologic films will show abnormalities in over 60 percent of patients. X-ray studies of the abdomen will frequently show hepatomegaly. X-ray films of the chest with lateral views may show elevation of the right hemidiaphragm, pleural effusion, basilar pulmonary infiltrates, atelectasis, or collapse and consolidation of the lung. By fluoroscopy the motility of the right hemidiaphragm may be reduced or abolished. Radioisotope liver scans, computerized tomography and ultrasound studies will usually make it possible to locate the lesion, determine its size and differentiate a solid from a cystic lesion. The gallium citrate scan may prove useful in differentiating an amebic from a pyogenic abscess.[16] The finding of increased gallium activity at the periphery of a large "gallium-negative" lesion has been described as aiding in the diagnosis of amebic abscess.[17] Barium meal and barium enema studies may be useful in showing changes in stomach contour and position, as well as pressure on the colon caused by an abscess of the left lobe of the liver. Invasive procedures such as arteriography are used infrequently.

Serologic Tests

A variety of serologic tests are both sensitive and specific.[2,3,18] If positive, they indicate current or past amebic infection and are, therefore, of greater usefulness in nonendemic areas. Antibody will be present only if there has been significant tissue invasion; thus, test findings are positive in over 95 percent of patients with amebic abscesses and 80 percent to 90 percent of those with severe intestinal infections. Generally, test results are negative in patients with asymptomatic intestinal infections. For tests that provide titers, the degree of seropositivity does not correlate well with severity of infection. In the United States two types of tests are commonly available: the indirect hemagglutination test at the Center for Disease Control in Atlanta (submit specimens through your local health department) and the agar-gel diffusion test which is carried out by local laboratories. The antigen is commercially available. The gel diffusion test, though somewhat less sensitive, is often of particular value because a report can be made available within 24 to 48 hours, when it is most needed in differential diagnosis of liver abscess or severe intestinal disease. The gel diffusion test becomes negative within two to three months of cure of liver abscess, but seroconversion by indirect hemagglutination test may take several years. Continuing asymptomatic intestinal infection is not ruled out by a negative gel diffusion test, but requires negative stool examinations as well. Two other tests available at some centers, counter current immunoelectrophoresis and cellulose acetate precipitin tests, can be conducted so rapidly that reports can be provided within hours. Further development of the enzyme-linked immunosorbent assay (ELISA) technique may permit detection of antigen in stool and in aspirates from liver abscesses.

Aspiration of Amebic Abscesses

The specific indications for aspirating an amebic abscess, and whether to do it percutaneously or during an exploratory surgical procedure continue to vary among authorities.[6,8-10,19-21] The main purposes of aspiration are to establish the diagnosis and to reduce the likelihood of rupture of a large abscess before drugs can be effective. Though it remains to be determined if evacuation of large lesions speeds their healing, it does immediately relieve pain and fever.

When the differential diagnosis between pyogenic and amebic abscess is in doubt, aspiration is indicated for diagnostic purposes.[6,8,9] Clinically diagnosed amebic abscesses, however, should not be aspirated for diagnostic purposes alone, be-

cause conservative medical management with a therapeutic drug trial is sufficient confirmation. However, if a good clinical response is not obtained within about three days, aspiration should be done. For large amebic abscesses, where there is danger of imminent rupture, most workers concur that aspiration is indicated for therapeutic purposes. The Durban group continues to aspirate amebic abscesses of all sizes if they can be reached percutaneously; this results in aspiration of about two thirds of their cases.[8] Nevertheless, it remains to be determined whether chemotherapy, in combination with aspiration of all abscesses, sufficiently reduces treatment failure rates to warrant the risks of the procedure.

An exploratory surgical operation is indicated (1) when inspection of a mass is needed before needling, (2) when an abscess that requires aspiration cannot be reached by a needle (especially abscesses of the left lobe) or if the needle fails to locate the abscess or (3) when under therapy the patient's condition is deteriorating or the quantity of pus is increasing. Repetitive puncture or punctures at multiple sites should not be done; drainage at laparotomy is safer.[9] The treatment of pyogenic abscess is surgical intervention with open and adequate drainage.[20]

Aspiration should be done under absolutely sterile conditions; the risks of the procedure are introduction of infection and hemorrhage; however, these risks are low. The patient should be mildly sedated and the skin anesthetized at the puncture site. Using radiologic studies as a guide for placement of the needle, enter at the site of greatest tenderness, or, if present, the point of skin edema or at the area of stony dullness to percussion. Use a number 20 needle equipped with a stop so the point can go no deeper than 8 cm to avoid inadvertent puncture of a portal radicle; change the direction of the needle no more than two to three times. When the abscess is located, change to a wide-bore needle and collect the fluid in aliquots. Only the final aliquot should be studied. Add to it 10 units of streptodornase per ml, incubate for 30 minutes at 35°C, centrifuge at 1,000 rpm for five minutes, and then examine both saline mounts and stained preparations. The aspirate should also be examined by Gram stain and cultured aerobically and anaerobically. The color of the fluid may vary from cream to yellow to green or chocolate. The fluid is relatively odorless in contrast to the foul smell of that from a pyogenic abscess.

TABLE 7.—*Partial List of Useful Antiamebic Drugs*

Tissue amebicides (act primarily in the bowel wall, liver or other extraintestinal tissues)
- Dehydroemetine, emetine
- Chloroquine (principally active in the liver)

Luminal amebicides (act primarily in the bowel lumen)
- Halogenated hydroxyquinolines: diiodohydroxyquin, iodochlorhydroxyquin
- Pentavalent arsenicals: glycobiarsol, carbarsone
- Alkaloids: emetine-bismuth-iodide
- Amides: clefamide, diloxanide furoate
- Antibiotics (act also in bowel wall): tetracyclines, paromomycin

Tissue and luminal amebicides
- Metronidazole

Differentiation of Amebic and Pyogenic Liver Abscess

Amebic and pyogenic liver abscesses are difficult or even impossible to differentiate[20,21] either

TABLE 8.—*Treatment of Amebic Liver Abscess*

Drug(s) of Choice	*Alternative Drug(s)*
(1) Metronidazole, 750 mg three times per day for 10 days,	(1) Dehydroemetine,* 1 mg/kg of body weight per day intramuscularly or subcutaneously for 10 days (maximum daily dose 0.1 gram), or emetine
followed by	*plus*
(2) Diloxanide fuorate,* 500 mg three times per day for 10 days, or diiodohydroxyquin, 650 mg three times per day for 21 days,	(2) Chloroquine, 500 mg (salt) twice per day for two days and then 250 mg twice daily for 26 days,
plus	*plus*
(3) Chloroquine, 500 mg (salt) twice daily for two days and then 250 mg twice daily for 12 days.	(3) Diloxanide furoate,* 500 mg three times per day for 10 days, or diiodohydroxyquin, 650 mg three times per day for 21 days.

*Available in the United States only from the Parasitic Disease Drug Service, Center for Disease Control, Atlanta, GA 30333. Telephone requests may be made by calling (404) 329-3670.

clinically or by laboratory and radiologic tests. When aspiration is indicated, it may provide the definitive diagnosis by detection and isolation of the causative agent. However, in most studies amebas are found in less than 50 percent of probable cases. Though the color of the aspirate is not a useful differentiating feature, the foul odor is characteristic of pyogenic infection but not of amebic abscess. In addition, few polymorphonuclear leukocytes are found in amebic aspirates. Some workers find trophozoites by histologic examination; specimens of wall tissue from the abscess are obtained by doing liver biopsies concurrent with diagnostic aspirations.

The most useful noninvasive test is serologic examination. Almost every patient with an amebic abscess will be serologically positive, and false-positive reactions are rare. Depending on the persistence of antibodies for the test used, a positive reaction in a patient from an endemic area could be misleading, and may only represent past intestinal infection, but not present disease.

Other factors and tests may or may not contribute to the diagnosis because the overlap is great. Patients with pyogenic abscess tend to appear sicker and usually have a higher leukocyte count, whereas patients with an amebic abscess tend to have a right lobe lesion, abnormal findings on chest x-ray studies, pleuritic pain and diarrhea. Results of liver function tests frequently give normal values or show low-grade abnormalities for both conditions, and multiple abscesses may occur for both. If jaundice is present it is more likely due to pyogenic abscess. Blood cultures should be done and may be positive with pyogenic abscess if sepsis is severe. A gallium scan and stool examinations for *E histolytica* should be carried out.

Medical Treatment of Amebic Liver Abscess

Medical treatment is highly effective. Death can usually be prevented if medical treatment (plus aspiration when indicated) is started early enough to prevent rupture. Table 7 lists drugs used to treat all forms of amebiasis according to their site of action as luminal and tissue amebicides.[22] Only metronidazole[23] is effective at both sites; it is, therefore, the drug of first choice for treatment of amebic liver abscess (Table 8). However, because it is not a highly effective luminal amebicide by itself, another luminal drug must also be used, such as diiodohydroxyquin or diloxanide furoate. Because there are occasional failures in treating amebic liver abscess with metronidazole alone, some investigators advocate following it with a two-week course of chloroquine. If metronidazole is not well tolerated, or if parenteral therapy is required, the older and alternate course of treatment is indicated—namely, combined usage of emetine (or dehydroemetine) and chloroquine. The alternate course should also be followed with a luminal amebicide. With either mode of treatment, the patient should show a clinical response within several days. Subsequent radiologic studies will usually show healing of the abscess with slow liver regeneration; generally, healing time ranges from two to ten months.[24] When relapses occur they usually appear within two months.

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Important Advances in Clinical Medicine

Epitomes of Progress — Pathology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in pathology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Endomyocardial Biopsy

BIOPSY OF THE kidney, liver or bone marrow is routinely carried out in clinical medicine. Endomyocardial biopsy now also has become a routine diagnostic procedure in many medical centers. Published techniques for obtaining myocardial biopsy specimens have included percutaneous needle biopsy of the left ventricle, open thoracotomy and catheter needle biopsy of the septum. The associated morbidity and mortality with these methods have precluded their widespread acceptance. The new method, a percutaneous transvenous biopsy of the endomyocardium using a modified catheter forceps, can now be done safely on an outpatient basis. More than 2,000 endomyocardial biopsies have been done at Stanford Medical Center. There have been no deaths, and the morbidity has been less than for renal or liver biopsies. The major complication is cardiac perforation and tamponade. In our series this occurred four times in more than 2,000 procedures; treatment was by pericardiocentesis and uneventful recoveries were made in each case. Other complications include transient atrial arrhythmias and transient nerve palsies relating to internal jugular vein puncture. The biopsy tissue is sufficient for light, electron microscopic and frozen tissue (immunofluorescence) studies.

For the first time this biopsy method has made possible the earliest detection of a cardiac disease process in living patients and has documented its reversal after treatment. Both left and right ventricular biopsies can be carried out with relative safety. Some of the indications for endomyocardial biopsy may be summarized: diagnosis and follow-up of treatment of myocarditis, diagnosis and treatment of rejection in cardiac transplant recipients, diagnosis of primary and secondary cardiomyopathies, (such as hemochromatosis or sarcoidosis) and differentiation between myocardial and pericardial restrictive cardiomyopathy (such as amyloid disease). More recently endomyocardial biopsy has been used for the diagnosis and monitoring of cardiotoxicity in patients treated with anthracycline for cancer. For this purpose a biopsy grading system is used for the early detection of those patients at risk for heart failure. The treatment can then be managed to prevent cardiomyopathy and ensure a maximum antineoplastic effect rather than depending on an arbitrary dose limitation. The advent of the

endomyocardial biopsy has enormous and exciting potential in both clinical and research applications.

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Billingham ME: Some recent advances in cardiac pathology. Hum Pathol 10:367-386, Jul 1979

Fine-Needle Aspiration Biopsy Cytology

CYTOLOGICAL DIAGNOSIS by fine-needle aspiration biopsy is a highly reliable, safe and inexpensive laboratory procedure. The advantages of needle aspiration biopsy include rapid diagnosis and simplicity with minimal discomfort and morbidity. A conclusive diagnosis of malignancy or etiological agent can usually be established without need to carry out open biopsy and frozen section of suspected lesions. For breast or superficial lesions, it is a feasible office procedure easily applied to patients with newly discovered palpable masses. At times, thoracotomy or laparotomy can be avoided. With the help of the image fluoroscopic intensifier in radiology, pulmonary lesions are accessible to the needle. With the guidance of ultrasound, biopsy specimens of deep abdominal or retroperitoneal masses can be taken.

An unequivocal diagnosis of malignancy may help physicians expedite necessary surgical therapy or it may influence therapeutic strategy in advance, making it possible to avoid less than ideal surgical procedures. For example, the cytological diagnosis of undifferentiated small cell carcinoma of the lung may be adequate for treatment by combined radiation and chemotherapy. Patients can be more completely informed before definitive surgical operation if this is desirable. The method has an overall diagnostic accuracy of 84 percent to 92 percent. A negative or a doubtful aspiration due to various reasons (such as faulty technique, poor sample or inexperience) must be followed by a repeat aspiration or an expeditious open diagnostic procedure to prevent a delay in appropriate treatment. False positive diagnoses have been reported to occur in up to 0.9 percent of aspirates.

The technique of aspiration sampling of palpable masses (breast, thyroid, lymph nodes and the like) and sonographically or radiologically visible lesions from different organs (lungs, pancreas, kidneys and so forth) is done with a 20-ml disposable syringe attached to a 22-gauge needle of appropriate length (1 to 4 inches). The use of an aspiration device (such as a Cameco syringe pistol, imported from Sweden by Precision Dynamics Corporation, Burbank, California) is preferred. The skin is first cleansed. Usually local anesthesia is not necessary. After the needle has penetrated the lesion, the syringe is retracted. Several short, quick lesional penetrations are done through the original puncture. Before the needle is removed, the vacuum in the syringe is equalized by releasing the piston. The needle is then withdrawn. The diagnostic specimen is in the needle, not in the syringe, unless fluid has been aspirated from a hollow organ, or a cystic or necrotic mass. Smears are prepared, fixed in 95 percent alcohol and stained with the method of choice. If clinically indicated, the specimen may also be cultured. Any tissue particle remnants should be fixed in formalin and submitted for a cell block histologic study to facilitate diagnostic accuracy and a possible typing of neoplasia.

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Neonatal Sepsis and Infective Endocarditis

ALTHOUGH THE CLINICAL PRESENTATION and antimicrobial therapy of infective endocarditis in infants are similar to those in adults, the events precipitating infection in neonates are often different and continue to change as medical technology advances. Although congenital heart disease is a known factor predisposing to infective endocarditis in infancy, in most reported cases of infective endocarditis in patients younger than 2 years old there is no preexisting heart disease. This prevalence of infective endocarditis in infants with normal hearts is partly related to the increased frequency of sepsis in these infants. With increased use of cardiac catheterization and hyperalimentation in this age group, there is in-

creased risk for introducing infectious organisms or dislodging valvular vegetations.

The clinical features are most often characterized by recurrent infections, with apparent adequate antibiotic therapy, until sudden severe cardiac decompensation occurs. Early identification of organisms is essential, but rarely does a well-documented sepsis precede the endocarditis. The appearance of a new cardiac murmur is of great therapeutic significance, but often it is not detected until late in the course of the infection, and frequently indicates impending cusp rupture. Congestive heart failure is associated with hemodynamically significant valvular regurgitation.

In contrast to findings in the adult population, an absolute as well as a relative increase in the number of children admitted to hospital with infective endocarditis is occurring. The most disturbing facts are that an antemortem diagnosis is rarely made, and there are few known survivors if infective endocarditis occurs before the age of 1 year. Therefore, early diagnosis and early adequate treatment of sepsis in young infants must be emphasized, along with continuing close observation for sufficient time to detect progression to endocarditis.

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Laboratory Investigation of Rape

THE PRESENCE OF SPERMATOZOA and elevated levels of acid phosphatase in the vagina are considered positive indicators of the presence of semen. Semen may also be identified by a semen-specific protein in cases of no sperm and low levels of acid phosphatase. The time of deposition of the ejaculate in the vagina is based not only upon sperm motility and their morphologic survival but also on quantitative levels of acid phosphatase. The latter is particularly useful in cases involving vasectomized men. Therefore, the minimum specimens for laboratory investigation of alleged sexual assault includes a microscopic examination for presence of sperm and motility as well as a quantitative acid phosphatase. Use of the Dacron swab technique allows for specimen collection from the vagina as well as the oral cavity, rectum, anal canal and body surface of an adult or a child.

Pubic hair combings as well as blood and saliva for ABO antigen secretor status when combined with the swab specimens have in selected cases been used for assailant identification or exclusion. Following a complete history, the proper and timely collection of pertinent specimens with adequate preservation and documented chain of possession is a *must* in cases of alleged sexual assault.

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Pneumoconiosis in Zoo Animals

SOME CASES of pneumoconiosis in humans suggest that atmospheric dust may play an etiologic role. To examine this possibility, animals have frequently been used as models of experimental pneumoconiosis. However, spontaneously occurring pneumoconiosis in animals is rarely reported. During the years 1956 through 1977, more than 11,000 autopsies were carried out on different species dying in the San Diego Zoo. A simple pneumoconiosis with lamellar birefringent crystals was observed in about 20 percent of the cases.

We studied 100 autopsies from 11 mammalian and 8 avian species. In mammals, mild pulmonary lesions comprised crystal-laden macrophages in alveoli and lymphatics. Interstitial fibrosis was present in 20 percent of cases. There were no nodules. In birds, dust retention produced large granulomas around tertiary bronchi without fibrosis. Mineralogic analysis using scanning and transmission electron microscopy showed most of the crystals to be silicates. About 90 percent were complex silicates with aluminum-potassium silicates comprising 70 percent of the analyzed particles. Electron and x-ray diffraction showed the silicates to be muscovite mica and its hydrothermal degradation product; that is, illite clay. This mica was also present on filtration membranes of atmospheric air samples obtained from the San Diego Zoo. The amount of dust retention

was related to an animal's age, anatomic or ecologic variances, and length of stay in the San Diego Zoo. Its semidesert atmosphere is rich in silicates which are inhaled and deposited in the lungs. Humans living in the same area may be exposed to the same risk, particularly if their occupation, such as agricultural work, makes them breathe a dustier atmosphere than other inhabitants of these areas. Since similar mica-induced lesions are found in men living in this region or the Southwest of the United States, this simple pneumoconiosis is likely to be widespread in human populations living in desert or semidesert climates.

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Use of Microprocessors in Microbiology

MICROPROCESSORS are miniature computers which can be packaged into a single integrated circuit measuring only 5 mm square. Their cost has decreased due to this miniaturization (now costing $15 to $20 for a central processing unit) so that an entire system may be installed economically into a medical instrument. These on-board microcomputers have led to applications in medical instrumentation that extend far beyond the scope of conventional circuitry. Instruments are appearing in which quality control checks, diagnostic troubleshooting, computations and data formatting are all under the control of a microcomputer. More recently, the computer capability in such instruments is being expanded to include simplified presentation of complex clinical data. These applications are currently emerging in microbiology—a field that has traditionally not been involved with automation.

Most recently in the field of microbiology, a microprocessor controlled instrument has been developed that can automatically read a tray of microtubes and report the results as a minimum inhibitory concentration (MIC). The MIC provides much more information than the traditional Kirby-Bauer disk diffusion method because it allows physicians to consider susceptibility in terms of a variety of antibiotic doses and sites of the body. This information, however, demands considerable interpretation by physicians because the MIC value must be compared with a table of achievable antimicrobic levels for different doses and sites of the body. It is now possible for a microprocessor to read an MIC value and compare it with a matrix of doses and body sites. A printout is then generated that clearly indicates whether a given antimicrobic is resistant, slightly sensitive, moderately sensitive or particularly sensitive for a given dose as well as a given site of the body.

The same microcomputer can provide microorganism identification in addition to reading an MIC and providing clinical interpretation. Various biochemical reactions can be determined in microtubes in the same plastic tray as an MIC determination. The reactions cause color changes in a battery of 21 to 27 biochemicals which form a profile or fingerprint characteristic of a given microorganism. Using observational probabilities stored in the memory of the computer, composite probabilities can be computed for each organism to an accuracy of one part in 4.3 billion. Results are then displayed and can be printed on the same form as the MIC results.

Microprocessor technology is expanding the capabilities of laboratory instruments to provide physicians with results that relate to known biochemical and pharmacological information.

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Screening for Alcoholism

IN VARIOUS HOSPITAL STUDIES, alcoholism was found in 3.7 percent to 9.9 percent of women and in 15.3 percent to 25 percent of men. In the general population, 5 percent to 10 percent probably have occasional problems with alcohol.

Five simple questions may alert the physician to alcoholism: "Do you drink?" If answer is no, ask "Could you tell me why?" This could reveal a temporarily abstinent problem drinker or alcoholic. If the answer is yes to drinking, ask "How (not why) do you drink?" This prevents the guarded or defensive reply, but gives a patient the opportunity to respond in any manner. Two further follow-up questions elicit problems associated with drinking. "Have you or close

family members been concerned about your drinking?" "Has drinking ever caused problems in your life?" A hidden or defensive alcoholic often begins to disclose a problem at this stage.

In the early diagnosis of alcoholism, the findings on physical examination may not be remarkable, but abnormalities are often present on laboratory testing. The following blood alcohol levels are diagnostic: (1) more than 100 mg per dl in a patient coming for a general examination; (2) more than 150 mg per dl without signs of intoxication and (3) more than 300 mg per dl at any time. A common abnormality is an elevated serum gamma-glutamyl transpeptidase (GGT) level two to four times normal. Less common is an elevated serum glutamic oxaloacetic transaminase (SGOT) value which will return to normal before the GGT level. Macrocytosis without anemia can develop during a long period of heavy alcohol drinking and requires months to resolve. Elevations can also be observed of triglycerides, serum bilirubin, alkaline phosphatase or uric acid. If a physician suspects that a patient is alcoholic, all these tests should probably be done. If results of *one or more* are abnormal, the patient can be confronted with the fact and told that the abnormality may be related to alcohol intake. Laboratory test abnormalities cannot be relied upon for diagnosis because there is a high rate of false negative determinations in alcoholic persons. The physician should have a reliable set of criteria for making the diagnosis.

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Jogging and Abnormal Laboratory Tests

VIGOROUS EXERCISE, such as jogging, can produce significant abnormalities in laboratory tests. Slight elevations in blood urea nitrogen, serum glutamic oxaloacetic transaminase, creatinine phosphokinase and lactic dehydrogenase have been found in routine physical examinations of persons who jog middle and longer distances (10 km or more). Gross hematuria may be observed in joggers and, more often, in marathon runners. Microscopic hematuria may be evident for up to one or two days. Cylinduria (3 to 5 casts per low power field) and proteinuria (2+ to 3+) has been observed in subjects within one hour after running a mile and a significant amount may still be present three to six hours after running. Usually these values return to normal after 24 hours.

Given the popularity of physical fitness activities and jogging today, a physician may need to be familiar with sports medicine and laboratory values for those who exercise vigorously. This knowledge may be essential in making sound clinical determinations about further clinical or laboratory studies.

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Screening for Neonatal Hypothyroidism

CONGENITAL HYPOTHYROIDISM lacks easily recognizable clinical features and is rarely suspected in the first few months of life. As a consequence, irreversible central nervous system damage may occur before the condition is recognized. Because treatment with thyroid hormone may prevent this damage if given before three months of age, early recognition is essential. Large scale population studies in Canada and England have shown an incidence of congenital hypothyroidism of approximately 1 per 5,000 live births.

Development of a reproducible and accurate technique for the determination of thyroxine (T_4) from a spot of dried blood on filter paper, similar to the technique used for phenylketonuria (PKU) screening, has made the test readily available for use in all newborn infants. The specimen is stable and the filter paper may be readily mailed. The testing is not time-dependent on ingestion of food as is PKU testing. The urgency is considerably less than for the PKU testing because immediate treatment is not as essential.

At present the procedure in most laboratories is as follows: The filter paper blood spot specimen is obtained from the newborn infant in the nursery at the same time and on the same filter paper as the PKU specimen. Alternatively, the test may be done on a liquid sample of cord blood. The specimen is tested for T_4 and results less than normal for the laboratory are consid-

ered as indicating possible hypothyroidism. The attending physician is immediately notified and a sample of serum for a thyroid stimulating hormone (TSH) study is requested. If the TSH level is elevated, a presumptive diagnosis of hypothyroidism is made. In hypothyroid infants a complete study is necessary to determine if the condition is transient or if it is primary hypothyroidism, pituitary or hypothalamic hypothyroidism, a deficiency of thyroxine binding globulin (TBG) or end-organ defect.

There is little question that identification of hypothyroidism in infants is of importance to state and federal governments because of the enormous costs of lifetime care of persons in whom the condition has not been identified. A program of required T_4 testing of newborn infants appears indicated by the significant incidence of this disorder. There is, however, considerable question about the advisability of establishing large government operated laboratories for diagnosis and counseling centers for care. This incursion into private medical practice does not seem needed or justified.

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Pap Smears—Lest We Forget

RECENT CRITICISM of cost effectiveness of routine Papanicolaou (Pap) tests has perhaps dampened the enthusiasm of the public, and in some cases physicians, about the need for routine gynecologic Pap tests. There may be value, therefore, in reviewing the history of this simple procedure and its effect on carcinoma of the uterine cervix.

From 1930 to 1974 age-adjusted cancer death rates for females indicated a drop in deaths from cancer of the uterus from first to fourth position, a decrease from 27 per 100,000 females to 8 per 100,000 females. In well-documented studies there has been a pronounced decrease in the cases of invasive cancer. In a 1956 study, 41 percent of the lesions detected were invasive. A 1979 study showed a 9 percent incidence of invasive lesions. From these data it becomes clear that tumors are being detected much earlier and in clinical settings where appropriate treatment for cure is possible. Routine Pap tests undoubtedly contribute to this favorable trend.

On the other hand, mortality data presented in a Minnesota study indicated 66 deaths in 1978 from cervical cancer (Cervical cancer deaths—Minnesota residents 1959-1978. Minneapolis, Minnesota Department of Health Center for Health Statistics, unpublished data). In spite of the widespread use of routine Pap tests, cervical cancer is still very much with us. The factors involved contributing to the continued incidence of death resulting from cancer of the uterine cervix are complex. Included are not carrying out Pap tests or pelvic examinations, inadequate or inappropriate treatment and inadequate follow-up. In 75 percent of the cases, patients are apparently responsible for inadequate care either by refusing pelvic examination or by not visiting a physician for routine annual examination or follow-up examination. In the other 25 percent of the cases physician responsibility was indicated in that pelvic examinations were not done, Pap tests were not carried out, or the reported histologic or cytologic findings were misinterpreted. The need for continued emphasis on physical examination, Pap tests and careful continued follow-up remains clear and cannot be overemphasized.

In recent years, cytology has become more of a diagnostic rather than a screening procedure, and the use of colposcopy in obtaining cervical biopsy specimens when there are abnormal Pap test results has increased the accuracy to approximately 99 percent. There is no excuse which can be justified by lack of *cost effectiveness* to forgive one undetected cancer of the uterine cervix.

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Recent Advances in Perinatal Clinical Chemistry

ONE OF THE most important decisions an obstetrician must make is whether or not to let nature take its course and have a baby delivered by natural labor or to preempt nature by inducing delivery. That decision is usually made on the basis of the maternal condition, the health of the fetus and the maturity of the fetus. Recent advances in clinical chemistry have contributed to

our evaluation of fetal health and the maturity. Three specific assays are critical in these evaluations: serum unconjugated estriol, serum human placental lactogen (HPL) and amniotic fluid surfactant measurements.

The serum estriol level is considered a measure of the fetoplacental function. The production of estriol comes about through a rather complex interplay of both fetal and maternal organs. A decreased estriol value, as compared with expected reference values, may often be an indication of a compromised fetus.

Serum HPL values obtained from maternal blood are directly related to placental size. Therefore, pregnancies associated with large placentas, such as in cases of maternal diabetes or multiple gestations (twins, triplets and so forth), will result in high HPL values. Maternal hypertension especially preeclampsia associated with fetal death will often result in very low HPL values. The fetal danger zone (FDZ) has been defined as HPL values in serum below 4 mg per liter after the 30th week of gestation. Many pregnancies associated with hypertension and fetal death will result in HPL values in this FDZ.

While the previously mentioned assays (estriol and HPL) will help an obsetetrician evaluate the health of a fetus, the amniotic fluid surfactant value will give an indication of fetal pulmonary maturity. Two major assays have been used to measure fetal pulmonary maturity: the lecithin to sphingomyelin (L:S) ratio and various foam stability tests. An L:S ratio greater than 2:1 will usually give assurance of fetal pulmonary maturity. The presence of surfactant in amniotic fluid will permit a mixture of amniotic fluid and ethanol to produce foam after being shaken. The presence of foam also gives such assurance of fetal pulmonary maturity. We have found great reliability in a new procedure called the foam stability index (FSI) test. This FSI assay presents the amount of surfactant in terms of the highest ethanol volume fraction which will permit foam to persist after being shaken.

In summary, we find that the serum unconjugated estriol level, serum HPL value and the FSI test result all contribute to a reasonable evaluation of fetal health and maturity. Based on these results and on the status of the pregnant woman, an obstetrician is well equipped to decide whether or not to induce labor or allow nature to take its course. Obviously other paraclinical measurements such as an oxytocin stress test, ultrasound measurements and the like, as well as information gained from a history and physical examination, also will play a role in this decision. Nonetheless, clinical chemistry has contributed much to assisting obstetricians in this decision.

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Immunohistologic Methods in Cell and Tumor Recognition

TRADITIONALLY, recognition of cell types and their corresponding neoplasms is based on the application of time-honored criteria passed down through preceding generations of histopathologists. As a result, the diagnosis of neoplasia is often hedged with uncertainty due to a continuing lack of positive methods with which to validate the morphologic criteria employed.

Cell identification may be enhanced by the use of special staining procedures, such as periodic acid-Schiff, methyl green-pyronine and trichrome stains, though these lack true cellular specificity, or by the application of exacting histochemical techniques that may be specific for cell-based enzymes but are of limited usefulness to diagnostic pathologists because of the requirement for fresh unfixed tissues.

The advent of a labelled antibody technique that is applicable to fixed paraffin embedded tissues thus offers significant advantages because it permits the demonstration of antigenic components within routinely processed material, which is often all that is available to pathologists when the need for special stains becomes apparent.

At present the most widely available of these immunohistologic techniques is based upon the use of horseradish peroxidase as a label for the site of tissue localization of the specific antibody. The specific antibody in turn serves to identify the distribution of the corresponding antigen within the tissue section. The immunoperoxidase technique has much in common with established immunofluorescence methods, with the same advantages of specificity and comparable sensitivity. Morphologic detail is, however, far superior to immunofluorescence and is equivalent to that obtained in routine hemotoxylin-eosin stains of formalin fixed paraffin embedded tissues. Using

light microscopy it is therefore possible to assess cell and tumor morphology critically in the face of an independent technique for positive cell identification, namely determination of the antigenic makeup of the cell.

The method is limited only by the availability of highly specific antisera and by the ability of the antigen in question to survive the rigors of tissue fixation and processing. The range of antisera available increases daily, and the many antigens that survive to a useful degree include immunoglobulins, J chain, lysozyme, ferritin, lactoferrin, transferrin, hemoglobin, α fetoprotein, α-1-antitrypsin, many polypeptide hormones, hepatitis B surface antigen, and other viral and microbial antigens.

An indexed bibliography of more than 600 immunoperoxidase papers is obtainable free of charge from Dakopatts, 22F North Milpas, Santa Barbara, CA 93103.

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The Two-Hour Oral Glucose Tolerance Test

THE AMERICAN DIABETES ASSOCIATION has recommended the standard two-hour oral glucose tolerance test (2-hr OGTT) as "yielding the most relevant diagnostic information." This test requires five venous blood specimens: fasting, ½ hour, 1 hour, 1½ hours and 2 hours. This routine is appreciated by patients. The recommended loading dose for adults is 75 grams; for children, 1.75 grams per kg of ideal body weight up to a maximum of 75 grams. This dose is more tolerable to patients and provides data that generally are interchangeable with those from the previous larger loading doses.

The interpretation criteria given in Table 1 are for the 2-hr OGTT venous plasma levels. Criteria for venous whole blood, capillary blood and blood from pregnant women, as well as a discussion of the new classification for diabetes mellitus disorders, can be found in the July 1979 issue of *Diabetes*.

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Prostatic Acid Phosphatase (Male PAP)

SUPPORT FROM THE clinical laboratory for the diagnosis of carcinoma of the prostate has relied heavily on the determination of the enzyme acid phosphatase. Until recent developments, the determination of acid phosphatase has been carried out kinetically utilizing various chemical substrates. The ubiquitous presence of this enzyme in tissues other than the prostate, such as bone, kidney, liver, spleen, pancreas and red cells, has placed limitations on the specificity (number of true positives associated with elevated enzyme levels) associated with this method. Various attempts to make the test more specific for prostatic disease through the use of inhibitors (tartrate, formalin) have met with limited success. The sensitivity of the test (ability to measure low

TABLE 1.—*Criteria for Interpretation of the Two-Hour Oral Glucose Tolerance Test*

Normal Levels	*Diagnostic of Diabetes Mellitus*	*Impaired Glucose Tolerance*
Nonpregnant Adults		
Fasting: <115 mg/dl 2 h value: <140 mg/dl ½, 1, 1½ h values <200 mg/dl	≥140 mg/dl 2 h value and one other (½, 1, 1½ h value) >200 mg/dl	<140 mg/dl 2 h value between 140 and 200 mg/dl and a ½, 1 or 1½ h value ≥200 mg/dl
Children		
F <130 mg/dl 2 h <140 mg/dl	≥140 mg/dl 2 h and an intervening value ≥200 mg/dl	<140 mg/dl 2 h value: >140 mg/dl

h = hour

levels of the enzyme in patients with carcinoma) has also been restricted by virtue of the kinetic assay. As a result of these limitations the ability of clinicians to detect the presence of prostatic carcinoma has been confined for the most part to patients with the more advanced stages of the disease: stage C (extracapsular extension) and stage D (metastatic spread).

These limitations provided the impetus for the isolation of an acid phosphatase specific to the prostate and the subsequent development of an antibody to this enzyme. The availability of an antibody allowed for utilization of the newer immunochemical techniques recently developed in the clinical laboratory, namely RIA (radioimmunoassay) and CIE (counterimmunoelectrophoresis).

The pronounced increase in sensitivity and specificity with these newer methods has been confirmed in various research centers as well as through the National Prostatic Cancer Project under the auspices of the National Cancer Institute. The initial data from various population studies have been very encouraging. Of those patients with prostatic carcinoma clinical stage A (intracapsular and nonpalpable), 38 percent were acid phosphatase positive by immunochemical techniques as opposed to only 12 percent detected by the more conventional chemical methods. Results are similar in persons with clinical stage B disease (intracapsular with a palpable nodule), 35 percent and 17 percent, respectively. Data such as these have created understandable enthusiasm for use of the immunochemical determination of prostatic specific acid phosphatase (male PAP) to screen the age group of highest prevalence, specifically men older than 50. False positives (up to 14 percent) do occur. This has been particularly true in patients after rectal examination or prostatic surgical procedures such as transurethral prostatectomy. In these latter instances, the false positivity, however, is transient.

The advantage the male PAP offers to clinicians is the ability to detect the presence of carcinoma of the prostate at a point in its clinical development when it is either occult or confined to the prostate. This in turn carries with it the theoretical possibility of improving the therapeutic result and concomitantly the prognosis.

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EDITORIALS

Power in the Health Care Enterprise

PRACTICING PHYSICIANS do not often think about power in the health care enterprise but others do, and a number of their assumptions about power fall short of the realities. Some have assumed that doctors have more power than they do and others assume that government has more power than it really has. Doctors, patients, families of patients, nurses, other health professionals, hospitals, payment agencies, professional associations, business, industry, labor unions, consumers and the public at large all exert significant power in and on the health care enterprise. And within the public sector power is also fragmented. Legislators make laws, the executive branches make regulations which have the force of law, and in the judicial branches the courts render their own decisions when matters are disputed and these also have the force of law. And then there are agencies, such as the Federal Trade Commission and the Occupational Safety and Health Administration (OSHA), that are virtually autonomous and can make and enforce rules to serve their own purposes. With so many loci of power it should not be surprising to anyone that laws and regulations imposed upon the system do not work well and that the health care field is rife with interactions within and between the public and private sectors, or that more often than not these are adversary in nature. Power in the health care enterprise is diffuse by any measure. It is also clearly without any central focus in either the private or public sector.

The above suggests that taken in the aggregate there is enormous power in the total health care enterprise but that it has yet to be harnessed as productively as might be. As a first step it would seem necessary to recognize that the power exists and that it is diffused in such a way that no segment or segments of power in either the private or public sectors are likely ever to be able to regulate or control the entire enterprise effectively. There is now a good deal of evidence that this is the case. Given this assumption (which may not be accepted by everyone) the next step would seem to be to recognize that the health care enterprise is actually a very complicated and complex interdependent system which really needs some governance of its relatively independent parts (some of which were listed above), if it is to run smoothly, be sensitive to human needs and be cost effective. If these can be accepted as givens, then it remains to find ways to mobilize the very considerable power that lies within the health care enterprise, and to direct it productively from within the system to the betterment of the system.

The adversary approach which now characterizes so many of the relationships among the system's independent yet interdependent parts is seldom productive, often wasteful and always costly. Rather, what is needed is exactly the opposite, a collaborative cooperative approach among parties at interest in both the public and private sectors, which would enable the power inherent in each of the independent parts to be brought to bear additively in pursuit of a common endeavor. This is not easily achieved, but when accomplished it can be enormously effective.

One senses that the name of the game may be changing, or has changed, and that the old rules are no longer working very well. Perhaps this is because growing social, economic, political and technical interpendence is bringing about irreversible changes in the way the game has to be played. If this is the case, as indeed it seems to be, then it is time to develop some new and more

cooperative approaches and some new rules of consensus agreement which will bring the power that exists within the health care enterprise more fully into play to identify and help solve some of the health care problems plaguing us all. This would be in both the patients' and the general public's interest. Medicine can and should take the lead. Perhaps the Voluntary Effort (VE) to control costs is at least a start at an approach that harnesses power from many loci within the system in a common endeavor about which there is consensus.

—MSMW

Mixed Connective Tissue Disease—An Evolving Clinical Syndrome

In 1972 Sharp and associates[1] described an "apparently distinct rheumatic disease syndrome" which was associated with autoantibody to a nuclear antigen, later characterized as a nuclear ribonucleoprotein (n-RNP) complex. Since that time there have been reports by many investigators defining and redefining mixed connective tissue disease (MCTD) and statements made for and against the existence of such a clinical entity. The report by Prystowsky elsewhere in this issue describes mixed connective tissue disease as perceived by an investigator in the dermatology clinic of the University of California, San Francisco, School of Medicine.

For the sake of future discussion in this field, terminology should be clarified. The original article used the term "extractable nuclear antigen (ENA)" as a convenient term to describe the nuclear antigen which was reactive with sera of patients with mixed connective tissue disease.[1] It has become clear that ENA consists of at least two nuclear antigens, n-RNP (which is destroyed by ribonuclease) and Sm antigen (which is *not* destroyed by ribonuclease).[2-4] Many other recently identified nuclear antigens are also as "extractable." These include the SS-B (Ha) and the SS-A nuclear antigens related to autoantibodies in Sjögren syndrome[5] and other extractable nuclear antigens related to autoantibodies in other connective tissue diseases. The use of "ribonuclease-sensitive ENA" to signify n-RNP antigen and "ribonuclease-resistant ENA" to signify Sm antigen is incorrect because there are multiple antigens in either category with these properties. The use of these terms has led to some misunderstanding, and one would be advised to characterize them as antibodies to n-RNP or to Sm antigen. In the mixed connective tissue disease, we are dealing with antibody to n-RNP, and it would be preferable to use this terminology rather than antibody to ENA.

In a previous study it was shown that antinuclear antibodies of different specificities were distributed in different connective tissue diseases in characteristic patterns.[6] Thus, antibody to Sm antigen was highly restricted to patients with systemic lupus erythematosus (SLE) and the concept was advanced that this antibody might be a serologic marker for SLE. On the other hand, antibody to n-RNP had a very wide distribution and was present not only in patients with mixed connective tissue disease, but also in high frequency in those with systemic lupus erythematosus, progressive systemic sclerosis and discoid lupus erythematosus; it was present in low frequency in several other connective tissue diseases. The important observation concerning antibody to n-RNP was clear—although it was present in patients with mixed connective tissue disease, it was not restricted to this disease, but was present in high frequency in patients with other connective tissue diseases as well. Therefore, if one examined patients in a lupus clinic and considered patients with high titers of antibody to n-RNP to have mixed connective tissue disease, there would be a high frequency of the clinical features of lupus. In an analogous fashion, there would be a high frequency of the clinical features of scleroderma, if one studied MCTD in a scleroderma clinic. This might explain why Prystowsky reports a high frequency of discoid lupus skin lesions (48 percent) in those patients who had high titers of antibody to n-RNP.

Nevertheless, the work of Prystowsky substantiates previous reports of other investigators in suggesting that there might be a constellation of symptoms which could constitute the mixed connective tissue disease syndrome. These reports have been consistent in pointing out a high frequency of Raynaud phenomenon in association with generalized, soft-tissue swelling of the fingers

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and hands. In Prystowsky's report, the Raynaud phenomenon was present in 93 percent and swollen hands in 50 percent of the patients. The clinical feature of generalized soft-tissue swelling of the hands and fingers should be distinguished from sclerodactyly, which is accompanied by hardening and thickening of the skin and subcutaneous tissues. These patients also had other manifestations of connective tissue disease such as arthritis and arthralgia, serositis, generalized lymphadenopathy and alopecia, as pointed out by Prystowsky. A low frequency of renal disease appears to be another characteristic clinical feature which might distinguish mixed connective tissue disease from systemic lupus erythematosus.

The accumulating evidence since 1972 clearly shows that antibody to n-RNP has a wide distribution in different connective tissue diseases and that features of systemic lupus erythematosus, discoid lupus, the Sjögren syndrome and scleroderma as well as rheumatoid arthritis have been observed in varying percentages of patients with mixed connective tissue disease. The real question is whether there is a clinical entity called mixed connective tissue disease. This question might be approached if investigators use both serologic as well as clinical markers to exclude patients with other connective tissue diseases. Clearly, patients with lupus and scleroderma have characteristic profiles of autoantibodies, and it is now possible with the aid of well-characterized serologic markers to identify and separate out systemic lupus erythematosus, progressive systemic sclerosis and, probably, other connective tissue diseases. There is precedence for the use of exclusions to classify connective tissue diseases, as exemplified in the American Rheumatism Association diagnostic criteria for rheumatoid arthritis.[7] There are indications that after overlap connective tissue diseases are separated out, there is an unusual group of patients who have high titers of antibody to n-RNP and whose clinical features do not fit into other classic connective tissue diseases. The practical importance of deciding this question is that a large percentage of these patients appears to respond well to the judicious use of corticosteroid therapy.

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Human Nature and Monetary Inflation

THERE IS growing evidence that the monetary inflation in this country has begun to feed upon itself. As wages and prices increase with inflation so do the dollars collected by government through such things as personal income, corporate and sales taxes. This produces little incentive for our public servants, whether elected, or appointed, or just plain hired, to reduce government spending even though this is generally believed to be a significant cause of the monetary inflation which seems to be getting out of hand so rapidly.

When one thinks about it, it seems obvious enough that there is a real conflict of interest for our public servants which has received relatively little attention. In or out of government human nature is much the same. One can therefore easily understand that our public servants, being human, are not likely to be very highly motivated to restrain or curtail the hand that feeds them, especially when it is feeding them rather well, and especially when what needs to be done is not necessarily going to be in the public servants' personal or bureaucratic interest—except to the extent they are all taxpayers and thus subject to the same economic pressures as are the rest of us.

It would seem that this conflict of interest is genuine, far-reaching in implication, and yet to be faced squarely. Conflict of interest has been made a big issue in many aspects of government, but so far not in this. But perhaps it is better that we not yet judge our public servants too harshly in this matter since we all share the same human nature—which we all know has yet to be perfected.

—MSMW

Familial Endocrine Tumors

MULTIPLE ENDOCRINE NEOPLASIA (MEN) syndromes, so clearly and concisely reviewed by Pont in this issue's Medical Progress section, are of special interest for many reasons, one being that unlike most endocrine tumors, these syndromes are familial. Since the discovery that there is a genetic predisposition for the development of one or more endocrine neoplasms, these syndromes have been the subject of extensive and rewarding study.

Although much remains to be learned about the pathogenesis of these tumors, several interesting observations have been made. Using as cell markers the electrophoretic pattern of glucose-6-phosphate dehydrogenase (G-6-PD), an X-linked isoenzyme, Baylin and co-workers have examined tissues from patients with medullary thyroid carcinoma and pheochromocytoma.[1,2] In females heterozygous for the A and B isoenzymes of G-6-PD, inactivation of one X chromosome, which occurs randomly during embryonic development, results in two cell populations in every tissue, one producing type A isoenzyme and the other type B. These investigators found only one isoenzyme in a given tumor, which indicated that the tumor arose from a single clone of susceptible cells and not from multiple cells. In one patient with medullary carcinoma, tissue from the tumor in the left lobe of the thyroid contained only type A isoenzyme and tissue from the tumor in the right lobe, only type B. Because in different tumors in this same patient there were different G-6-PD isoenzymes, the investigators proposed that neoplasms in the MEN II syndrome arise from two mutational events—an initial inherited mutation produces multiple clones of susceptible cells and a final mutation in one clone of these cells results in tumor formation. The nature of the factor or factors that produce the final mutation remains unknown and may be distinct for each organ. Moreover, there is a growing body of information supporting the concept that in multiple endocrine neoplasia, hyperplasia precedes neoplastic transformation. The progression of hyperplasia to malignant lesions is most clearly documented in medullary carcinoma, although the chronologic position of hyperplasia in this postulated sequence of tumorigenesis has not been clarified. The disparity in neoplastic transformation to medullary carcinoma (a malignant tumor in the thyroid) and to pheochromocytoma (a tumor which is usually benign in the adrenal) of cells that share the same basic inherited defect is another intriguing aspect of this syndrome.

Of immediate importance in the care of patients and families with multiple endocrine neoplasia are the advances that have been made in early diagnosis and treatment of these syndromes, especially MEN II (medullary carcinoma, pheochromocytoma and hyperparathyroidism). The immense progress that has been made in understanding and treating this syndrome serves as a stimulus in the continuing search for biochemical markers for other tumors. To give a sense of perspective, a brief review of some of the accomplishments in the study of this disease over the past 20 years is in order.

In 1959 medullary carcinoma was recognized as an entity distinct from other types of thyroid cancer. In the 1960's the following strides were made: a strong familial tendency and a frequent association with pheochromocytoma and hyperparathyroidism were noted; the cellular origin of the tumor from the parafollicular or C cells was established, and a highly specific and sensitive biochemical tumor marker, calcitonin, was identified. In the 1970's the measurement of calcitonin in peripheral blood by radioimmunoassay proved to be of extreme value in the diagnosis of medullary carcinoma and management of patients. Calcitonin levels, basal and stimulated, have permitted detection of occult tumors much earlier than was possible with conventional diagnostic techniques, such as palpation and radioisotope scanning, that have been applied to evaluating tumors of the thyroid. Early detection of medullary thyroid carcinoma has resulted in fewer patients having metastasis to regional lymph nodes at the time of surgical operations. Prognosis has been improved, and cure is now possible.

The potential benefits of early detection of medullary carcinoma justify an aggressive approach to screening patients known to be at increased risk. The basic defect is inherited as an autosomal dominant trait with a high degree of penetrance, so that approximately 50 percent of a patient's siblings and children will, therefore, be affected. In addition to annual testing of all family members of patients with MEN II, initial family screening appears warranted in patients

with medullary carcinoma presumed to be sporadic. Sizemore and co-workers surveyed 219 primary relatives (siblings and children) of 36 patients with medullary carcinoma and no family history of thyroid tumor, pheochromocytoma or hyperparathyroidism, and identified 57 affected members in seven families.[3] Because not all relatives were tested, the frequency of familial medullary carcinoma in patients with tumors presumed to be sporadic on the basis of the patients' histories is probably higher than the 19 percent reported. Calcitonin testing should also be carried out in all patients in whom the diagnosis of pheochromocytoma is made and in anyone found to have hyperparathyroidism due to multiple gland involvement. Initially, it appeared that elevated calcitonin levels were diagnostic of medullary thyroid carcinoma. Subsequently, however, ectopic production by a variety of tumors has been reported, and, occasionally, elevated calcitonin levels occur in nonmalignant disorders. Although this possibility must be considered, the clinical presentation usually permits these conditions to be easily excluded.

Screening tests for patients and families with MEN I (hyperparathyroidism, islet cell tumors and pituitary adenomas), as indicated in Dr. Pont's paper, are complex. As with any test, interpretation is best accomplished when correlated with a patient's clinical presentation. The diagnosis of hyperparathyroidism, even though asymptomatic, presents little difficulty and the vast majority of patients with functioning islet cell tumors have characteristic symptoms. Diagnostic problems may, however, be encountered in early detection of pituitary tumors. Prolactin measurements have proved to be extremely valuable in the diagnostic study of patients with suspected pituitary tumors. Antunes and colleagues studied the cases of 47 patients with nonfamilial pituitary tumors.[4] Serum prolactin concentration was elevated in 79 percent. Even when patients with galactorrhea were excluded, hyperprolactinemia was present in more than 65 percent. Although experience with prolactin determinations in the MEN I syndrome is limited, it is very likely that a similar prevalence of hyperprolactinemia will be found.

Initial evaluation of high-risk patients should include examination of visual fields and tomography of the sella turcica. If findings from either are abnormal, pituitary function should be assessed in women with galactorrhea, oligomenorrhea or amenorrhea, and in men with impaired libido or potency. While tomograms of the sella turcica are superior to plain films in diagnosing early pituitary tumors, their interpretation remains controversial.[5] A sella turcica with slight asymmetry or with a double floor should not be considered pathologic unless associated thinning or erosion of the lamina dura or destruction of bony structures is present. The accuracy of radiologic diagnosis of pituitary tumors is improved when endocrine studies corroborate. In the absence of pituitary hormone hypersecretion as reflected by peripheral blood hormone levels, or hypopituitarism confirmed by abnormal response to stimulation tests, the diagnosis of a pituitary tumor by sella tomography alone is tenuous. The growth of pituitary adenomas is slow. If findings of initial screening studies are within normal limits, it is usually not necessary to reevaluate pituitary status more frequently than every two or three years. Because of potential cataract formation related to cumulative radiation, follow-up tomograms of the sella turcica should be ordered judiciously.

The information obtained from the study of patients with multiple endocrine neoplasia syndromes has importance for practicing physicians and investigators alike. By applying the tests, as clearly outlined in the review, early diagnosis and treatment of tumors that would otherwise be lethal is now possible. The success of using biochemical markers for the detection of tumors should encourage more extensive investigations of this kind.

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CASE REPORTS

Refer to: Platia E, Vosti KL: Noncholera vibrio septicemia. West J Med 132:354-357, Apr 1980

Noncholera Vibrio Septicemia

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NONCHOLERA VIBRIOS (NCV), sometimes called nonagglutinable vibrios, are classified microbiologically as *Vibrio cholerae,* and are in fact biochemically indistinguishable.[1] They are differentiated by the inability of noncholera vibrios to agglutinate in vibrio group I antiserum;[2] *V parahaemolyticus, V alginolyticus* and other halophilic vibrio species are biochemically distinct. Clinical disease caused by NCV has been reported infrequently. A recent review from the Center for Disease Control compiled a total of 28 cases of patients with isolates, mostly from the stool, identified as noncholera vibrio.[3] Hughes and coworkers noted that the incidence of infection with NCV appeared to be rising in the United States over the past decade, perhaps related to ever increasing foreign travel and other factors.[3] We report the case of a patient with chronic lymphocytic leukemia in whom noncholera vibrio septicemia developed upon return from a trip to the Far East.

Report of a Case

A 67-year-old man with a six-year history of chronic lymphocytic leukemia was admitted to hospital for evaluation of fever, chills and left-sided facial pain. Except for a long history of peptic ulcer disease, with a partial gastrectomy in 1965, he was in good health until 1972, at which time the diagnosis of chronic lymphocytic leukemia was made. Treatment without chemotherapy was begun and the patient did well until 1977, when administration of chlorambucil and prednisone was initiated because of a leukemic, pulmonary infiltrate. The patient's condition improved. In late 1977, he noted the occurrence of frequent furuncles on his trunk and extremities and had one episode of facial cellulitis. Analysis of immunoglobulin disclosed hypogammaglobulinemia, with a substantial decrease in IgG and IgA (γ-globulin 300 mg, IgG 200 mg [normal 800 to 1,800 mg] and IgA 25 mg [normal 90 to 450 mg]). Skin tests with mumps, *Candida, Trichophyton* and tuberculin antigens showed him to be anergic. Monthly intramuscular injections of γ-globulin were begun. In late May 1978, paranasal sinusitis developed with pronounced facial pain and purulent nasal drainage from which *Staphylococcus aureus* was isolated. He was treated with oral administration of dicloxacillin for three weeks with apparent resolution.

In June 1978 the patient received a ten-day cycle of chlorambucil and prednisone before embarking on a three-week pleasure trip to Hong Kong, Taiwan and the Philippines. A month before leaving he received cholera and smallpox immunizations. On June 30, 1978, while in the Philippines, he noted the onset of loose, liquid, brown stools, occurring four to six times per day. He said that he did not eat raw foods but admitted to frequent meals of seafood and ad libitum consumption of local water. His wife, who accompanied him and ate a similar diet, remained well. Left-sided facial pain and tenderness had returned shortly after departing on his trip and continued to grow worse.

Upon his return to California on July 4, 1978, he went directly to the hospital for admission, as he felt that his paranasal sinusitis had returned. Although low-grade diarrhea was still present and unabated, he did not consider it to be a major problem. On admission he appeared chronically ill and emaciated, and frequently complained of pain in the area of the paranasal sinuses. Vital signs were a temperature of 38.3°C (100.9°F), pulse rate of 100 and respiratory rate of 20 per minute and blood pressure of 130/65 mm of mercury. A physical examination disclosed bilateral percussion tenderness over the frontal and maxillary sinuses and bilateral purulent nasal dis-

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charge, the left side being greater than on the right. Lymph nodes in the axillary and inguinal regions were moderately enlarged. Examination of the chest and heart showed no abnormalities. The abdomen was soft and not tender, with audible bowel sounds and a palpable spleen 5 cm below the left costal margin. On neurological examination the patient gave sluggish responses but he was oriented and without focal signs.

Laboratory studies on admission included a hematocrit of 33 percent, and a leukocyte count of 10,000 per cu mm with 3 percent bands, 25 percent polymorphonuclear cells and 72 percent lymphocytes. Automated SMA-6 and SMA-12 profiles were within normal limits. Analysis of urine, an x-ray study of the chest and an electrocardiogram were similarly unremarkable. Sinus x-ray studies showed opacification of both maxillary sinuses with air-fluid levels. Gram stain of the nasal discharge showed many polymorphonuclear cells and Gram-positive cocci in clumps. The stool was liquid, brown and guaiac-negative, fecal leukocytes were absent, and no ova or parasites were seen.

A preliminary diagnosis of staphylococcal sinusitis was made. After cultures of blood, stool and nasal discharge were obtained, the patient received nafcillin intravenously, 12 grams per day in six divided doses. Bilateral lavage of the maxillary sinuses was done, with drainage of much purulent material. Cultures of the sinus drainage grew *S aureus,* blood cultures were negative and stool cultures were reported as negative for enteric pathogens. Within 24 hours his fever defervesced, and after several lavages of his sinuses he felt much improved. The low-grade diarrhea persisted in hospital, and on hospital day 4 the patient again began to have a low-grade fever. An x-ray study of the abdomen was remarkable only for several calcified gallstones, and several stool cultures were again reported as negative for enteric pathogens. On the ninth hospital day he became febrile with a temperature of 39.5°C (103.1°F) and pronounced chills, rigors and diffuse abdominal cramps. Chloramphenicol was added to his regimen of intravenous administration of nafcillin, after several blood cultures were drawn and a spinal puncture done. Examination of the spinal fluid gave normal values and a culture was sterile. The following day, both blood cultures grew a vibrio species biochemically identical to *Vibrio cholerae,* but nonagglutinable in 0:1 antiserum.[6] These results were confirmed by the county and state laboratories. The organism was sensitive to clindamycin, ampicillin, chloramphenicol, tetracycline, gentamicin and tobramycin. Within 24 hours of the initiation of therapy with chloramphenicol, the patient became afebrile, without abdominal pain and with resolution of his diarrhea. Shortly thereafter, numerous stool cultures were taken again in repeated attempts to isolate noncholera vibrios. These were unsuccessful. Nafcillin therapy was discontinued after a 14-day course, and chloramphenicol was administered for two weeks. Tetracycline was not given because of a reported allergic reaction in the past. The patient remained free of symptoms for several days after discontinuation of antibiotics, and was discharged. At a one-month follow-up visit to the clinic, he was doing well.

Discussion

Dutta and co-workers[4] first reviewed the choleragenic nature of certain nonagglutinable strains of *V cholerae* (NCV) in 1963, and were able to induce a cholera-like disease with them in infant

TABLE 1.—*Clinical Features of Patients With Noncholera Vibrio Septicemia*

	Patient (Reference)			
	1 (Present Report)	*2 (Hughes[3])*	*3 (Hughes[3])*	*4 (Hughes[3])*
Age/sex	67/M	72/M	64/M	56/M
Residence	California	Kentucky	North Carolina	Texas
Exposure to NCV	Travel to Philippines	Salt water	Salt water	Unknown
Diagnosis	Diarrhea, fever	Pneumonia, Gram-negative sepsis	Cellulitis, meningitis, Gram-negative sepsis	Gram-negative sepsis
Associated diseases	Chronic lymphocytic leukemia	Acute monocytic leukemia	Severe peripheral vascular disease	Cirrhosis
Treatment	Antibiotics	Antibiotics, steroids	Antibiotics, steroids	Unknown
Outcome	Survived	Died	Died	Died

NCV=noncholera vibrios

rabbits. McIntyre and colleagues[5] in 1965 reported a series of 19 patients at the Cholera Research Laboratory in Pakistan with NCV isolated from their stools. Some patients presented with a syndrome of fulminant diarrhea, some with a cholera-like illness with voluminous, watery stools, requiring intravenous fluid replacement therapy, and others presented with a mild illness requiring no therapy. Similarly, in the report by Hughes and co-workers[3] on isolates of NCV which had been referred to the Center for Disease Control, most of the patients had an acute diarrheal illness with positive stool cultures, and survived. However, three of their patients had positive blood cultures for NCV and all died; one of these patients was reported previously in 1974. Of interest, all three of the patients with bacteremia had a significant and chronic associated disease, including one man with acute monocytic leukemia. The clinical features of these three patients are compared with those of our patient in Table 1.

Our patient, too, presented with an acute diarrheal syndrome of low-grade nature of a week's duration though his primary complaint was facial pain referable to an apparent paranasal sinusitis. Treatment directed toward the *S aureus* that had been obtained from his sinus discharge was followed by improvement of the sinusitis. However, the low-grade diarrhea and crampy abdominal pain continued in hospital, though not particularly impressive in nature. However, a week later, after multiple negative stool cultures, the patient appeared clinically septic, with high fever and rigors, and NCV was grown from several blood cultures. It is difficult to explain why the NCV organism could not be isolated from the patient's stool at any time throughout his illness. One possibility is that NCV was indeed present in the stool but was not identified in the laboratory. Most strains grow on MacConkey agar in 18 to 24 hours, but form minute, colorless colonies which can be overlooked.[6] After the NCV was isolated from the patient's blood, special efforts were made with selective thiosulfate-citrate-bile salts-sucrose media to culture the organism from the stool, but without success—perhaps because antibiotics had been administered previously. It should be noted that the organism might have been harbored in the patient's diseased gall bladder. Some evidence exists that in chronic carriers of *Vibrio cholerae,* the organism may be sequestered in a diseased gall bladder with stones.[7]

Also of interest was the continued low-grade diarrhea for two weeks before our patient's episode of sepsis, rather than an acute, short bout of voluminous diarrhea. This may have been related to the patient's status as a compromised host, as discussed below. He did appear to respond adequately to antibiotic therapy with chloramphenicol, with defervescence and gradual resolution of his diarrhea. The role of antibiotics in the treatment of noncholera vibrio infections remains to be established clearly; however, appropriate antibiotics, particularly tetracycline, have been shown to decrease the severity and duration of symptoms in patients with cholera, and it has been suggested that they may have some effect on intestinal infections caused by NCV.[3,8]

Several factors might have contributed to our patient's status as a compromised host. First, his general nutritional state was poor, with chronic anorexia and weight loss. Second, the patient showed evidence of depressed T cell and B cell function, exhibiting anergy to all skin tests and hypogammaglobulinemia, with substantially depressed IgA and IgG. Secretory IgA coproantibody is thought by some to be involved in local antibacterial immunity in infections with *Vibrio cholerae.*[7] It seems reasonable to assume that our patient's secretory antibody might have been quite low. The effectiveness of the cholera vaccine is uncertain, however, because of his hypoglobulinemia it is likely that he may not have responded to the vaccine anyway. Finally, the patient's previous partial gastric resection for peptic ulcer disease and his continued chronic use of antacids may have increased his predisposition to enteric bacterial diseases. The potential importance of the antibacterial effect of gastric acid in the prevention of enteric bacterial diseases, including cholera, has been observed in volunteers in whom a decrease in the size of the inoculum required for infection followed a decrease in gastric acidity with sodium bicarbonate.[8]

Summary

We report a case of noncholera vibrio septicemia of presumed gastrointestinal origin in a man with chronic lymphocytic leukemia who became ill while on a trip to the Far East. His illness was characterized by low-grade diarrhea and abdominal cramps, and septicemia with sudden high fever, chills, and rigors developed two weeks after the onset of symptoms. The occurrence and presentation of his disease may have been related to his leukemia and its treatment, poor nutritional

state, depressed T cell and B cell function, or previous partial gastrectomy. He responded well to antibiotic therapy with chloramphenicol and general supportive measures. To our knowledge, he represents only the fourth reported case of noncholera vibrio septicemia, and is the only such case to have survived.

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ABBREVIATIONS USED IN TEXT

DPH = diphenylhydantoin
GLI = glucagon-like immunoreactive

Inhibition of Glucagon Secretion by Diphenylhydantoin in a Patient With Glucagonoma

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DIPHENYLHYDANTOIN (Dilantin, phenytoin, DPH) has been shown to inhibit glucagon secretion in vitro.[1] The drug also inhibits insulin secretion in vitro and in humans.[2-7] The glucagonoma syndrome is characterized by dermatitis, stomatitis, elevated plasma glucagon levels, abnormal glucose tolerance, weight loss and anemia.[8,9] The effects of DPH therapy were investigated in a patient with surgically documented glucagon-producing tumors and substantially elevated levels of glucagon in serum.

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Report of a Case

A 49-year-old woman entered the hospital with a six-week history of extensive exfoliative, migratory dermatitis on the lateral aspects of her extremities, buttocks, back and face. She had lost weight, her mental status had deteriorated, and intermittent diarrhea, generalized weakness and stomatitis had occurred. A glucose tolerance test at another hospital showed a fasting plasma glucose level of 130 mg per dl and a two-hour postprandial value of 200 mg per dl. There was no family history of diabetes or endocrine disorders.

The physical examination showed a normotensive, afebrile, ill-looking woman with an extensive, coalescing, erythematous rash characterized by hyperpigmentation, scaliness and areas in various stages of healing. Results of a fundoscopic examination were normal. There were oral fissures and moderately severe glossitis. There were no abdominal masses. The legs were slightly edematous.

Findings of initial laboratory studies included a fasting plasma glucose level of 137 mg per dl, normochromic anemia and levels of serum lipids within normal range. The urine was positive for ketones but showed no glycosuria. Findings of baseline endocrine studies, including thyroid and adrenal functions, were normal. Biopsy of a skin lesion from the forearm showed a nonspecific perivascular, lymphocytic infiltrate with edema and hyperkeratosis. Fasting plasma glucagon level was 3,612 pg per dl (basal measurement in six normal subjects was 162 ± 21 pg per dl [mean ± SD]), using a pancreatic glucagon-specific antibody,

30K Unger. Some 66 percent of plasma glucagon chromatographed (Bio-Gel P-10) with "true" pancreatic glucagon (molecular weight of 3,500); however, about a third was in a larger form (laboratory of Dr. Roger Unger).

Upper gastrointestinal roentgenograms showed swollen gastric and duodenal mucosal folds, and the transit time was prolonged. A liver scan showed a diffusely enlarged liver with an abnormal periportal filling defect. Results of pancreatic scan and abdominal ultrasound examination were not conclusive. Celiac axis and superior mesenteric arteriography showed a tumor blush in the head and tail of the pancreas, and an isolated area of tumor blush in the right hepatic lobe.

During surgical operation a spherical lesion 3 by 3 cm was found in the head of the pancreas, as well as multiple lesions in the tail. A single 7-cm spherical liver metastatic lesion was also found. Following removal of 95 percent of the pancreas and resection of the metastatic tumor, cardiovascular collapse and cardiac arrest occurred. The patient died three days after the operation.

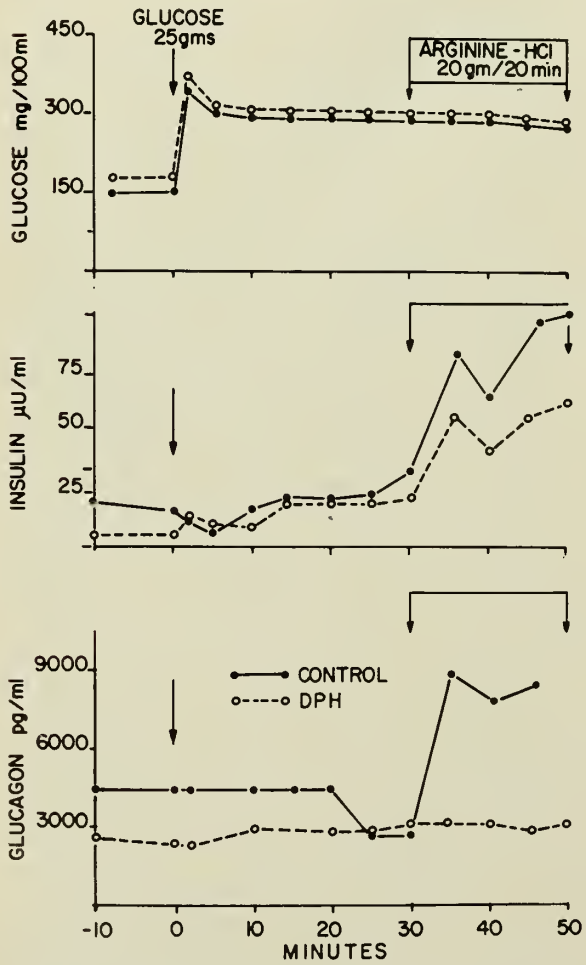

Figure 1.—Basal and stimulated glucose, insulin and glucagon levels in a patient with glucagonoma syndrome before and after diphenylhydantoin (DPH) administration.

Microscopically, the homogeneous, encapsulated tumor had anastomosing islands and cords of cells with no cellular or nuclear aplasia. Immunofluorescent antibody studies (laboratory of Dr. Lelio Orci) on segments of tumor tissue from the pancreas, showed cross-reactivity with nonspecific antiglucagon sera (98J Unger) and anti-GLI-1 serum, Moody R-64 (anti-Glicentin), but not with pancreatic glucagon-specific antisera (30K Unger, 50K Unger).

Methods

After an overnight fast with maintenance on a 2,400 calorie diet for three days, a needle was inserted intravenously into the patient's forearm and baseline specimens were drawn for an hour. The protocol consisted of a 25-gram glucose tolerance test carried out intravenously, followed after 30 minutes by an arginine infusion of 20 grams over 20 minutes.[2] Specimens were collected every five minutes for plasma glucagon, serum insulin and plasma glucose. The patient was treated for seven days with 200 mg of diphenylhydantoin given orally, three times a day, until slight nystagmus occurred. The test was then repeated and the level of serum DPH at that time was 15μg per ml, considered to be in the therapeutic range for patients with seizure disorders.[10] Levels of serum glucose[11] and serum insulin[12] were measured by standard methods. The plasma glucagon level was measured using 30K antisera.[13]

Results

On the day of the control study, before DPH treatment (Figure 1), the baseline glucose measurement was 152 mg per dl. The glucose disappearance rate was low, with a K value[14] of 0.7 mg per dl per minute. Serum insulin level did not rise from the basal measurement of 33.9 μU per ml after administration of glucose. However, after arginine infusion, the summated serum insulin level, derived from adding values obtained at 35, 40, 45 and 50 minutes[2] was 449.8 μU per ml. Basal plasma glucagon level was elevated to 3,688 pg per ml and was suppressed 25 minutes following a glucose load, to 1,972 pg per ml. With arginine infusion, plasma glucagon level

rose substantially to a peak of 8,000 pg per ml. Table 1 describes basal plasma glucagon and serum insulin levels on four separate days before administration of DPH.

After DPH treatment (Figure 1) baseline plasma glucose level was 161 mg per dl and the glucose clearance rate remained abnormally low, with a K value of 0.5 mg per dl per minute—essentially unchanged compared with values before drug administration. Serum insulin levels decreased to 7.8 μU per ml basally and then rose to 19.7 μU per ml at 20 minutes after intake of glucose. The summated serum insulin level was 263 μU per ml after arginine, which was somewhat reduced, compared with values before DPH therapy. Baseline glucagon level was decreased to 2,395 pg per ml and the plasma glucagon response to arginine was eliminated. After DPH therapy, the basal plasma glucagon levels fell below 2 SD from the mean levels determined (Table 1) on four separate days before administration of DPH. This was also true for the basal measurement of insulin. Symptoms were not changed by DPH.

TABLE 1.—*Basal Values Before Diphenylhydantoin Therapy*

Date	*Glucagon pg/ml*	*Insulin μU/ml*
10/7	3,612	42.7
10/8	3,688	33.9
10/10	4,000	24.6
10/15	3,248	32.4
MEAN±2 SD	3,637±618	33.4±14.82

Discussion

A patient with a surgically documented glucagonoma and with elevated levels of plasma-immunoreactive glucagon was treated with DPH. This resulted in a decrease in basal plasma glucagon level and a reduced plasma glucagon response to arginine. This inhibitory effect of DPH may arise from changes in α-cell membrane cation-dependent enzyme (adenosine triphosphatase) activity.[15] These data suggest that DPH, in nontoxic levels, may partially inhibit the excessive secretion of glucagon in this condition, without altering glucose levels or glucose clearance. Failure to lower plasma glucose levels when circulating glucagon was reduced may have been related to suppression of serum insulin levels in our patient. However, apart from effects upon plasma glucose, the glucagon levels seen in this patient would be expected to bring about negative nitrogen balance,[16] proving deleterious to patients undergoing surgical operations for this condition. Diphenylhydantoin, by suppressing glucagon, might be used as an adjunct to antidiabetic treatment, with or without somatostatin,[17] in preparation for an operation, or when a glucagonoma cannot be excised.

The predominance of glucagon-like immunoreactive (GLI) material in this patient's tumor, associated with pronounced "true" glucagon (molecular weight of 3,485) immunoreactivity[13] in plasma is a point of interest. The material detected in the tumor by antibody R-64 (Moody) is very similar to a glucagon-like hormone originating from the gut. GLI reactive material has been found in pancreas,[17] and one current theory[18,19] suggests that biosynthesis of glucagon might proceed through a molecule having chemical similarities to GLI. Thus, a possibility is that the elevated plasma glucagon (30K antibody reactivity) levels found in our patient's plasma, as well as some biological activity, resulted from a GLI precursor. Another consideration is that the highly elevated levels of GLI cross-reacted with 30K antibody to result in what appeared to be increased levels of "true" glucagon. Because the patient had a rather typical glucagonoma syndrome, biologically active molecules were produced. Recent evidence has suggested[20] that peptides secreted by tumors may share a common precursor (molecular weight of 65,000) which could contain antigenic sites of several hormones. Moreover, there is evidence[21] that molecules as large as 9,000 daltons can share antigenic sites with 3,500-dalton glucagon and be measured in glucagon assays in plasma of patients with glucagonoma syndrome. It may be that this patient's tumor cells contained peptides with antigenic sites which could react with a variety of antisera.

The peptide somatostatin has effects which are qualitatively similar to those of DPH. These effects have been studied in glucagon-producing islet cell tumors. For example, Tiengo and co-workers[22] produced a lowering of glucagon from 2,300 to 1,400 pg per ml (39 percent), with simultaneous lowering of insulin and glucose levels. Mortimer and colleagues[23] suppressed glucagon to 340 pg per ml from basal levels of 948 pg per ml (64 percent). In our patient, reduction of plasma glucagon concentration from a mean basal level of 3,637 to 2,395 pg per ml (34 percent) approximated effects of somatostatin. Moreover, when somatostatin is stopped, plasma glucagon

returns to the basal level. Effects of DPH would be expected to be less evanescent because DPH persists in serum for two to three days after discontinuation of the drug.[10]

DPH therapy has been tried in at least one other case of glucagonoma syndrome,[24] without effects on glucagon levels. However, the authors did not state how long the drug was given before taking glucagon measurements, nor did they report serum DPH levels. Both the neurologic effects and effects of insulin secretion may depend on serum levels. Furthermore, just as the ability of DPH to inhibit insulin production in the insulinoma syndrome can vary from patient to patient,[3] so might the drug have variable effects on islet cell tumors which secrete glucagon.

Summary

The antiepileptic drug diphenylhydantoin (DPH) was given to a patient with glucagonoma syndrome. The baseline level of immunoreactive glucagon in plasma was very high (3,618 pg per ml) and increased substantially with arginine stimulation (8,000 pg per ml). After DPH treatment, baseline plasma glucagon concentration was reduced and the rise in plasma glucagon after arginine infusion was totally inhibited. Basal and arginine-induced insulin secretion were inhibited without alteration of glucose levels or glucose clearance. These findings suggest that DPH has effects on glucagon and insulin which are qualitatively similar to those of somatostatin.

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Orthodox Medicine Humanistic Medicine Holistic Health Care

In the December 1979 issue the editors of The Western Journal of Medicine began a forum for dialogue and discussion of orthodox medicine, humanistic medicine and holistic health care. The forum was initiated with statements by persons known to have an interest in and knowledge of this subject, and readers were invited to submit their views constructively and succinctly. All of the material, published and unpublished, will be collated and, if possible, a distillate will be prepared to summarize the dialogue and discussion.

—MSMW

A Comprehensive Approach to Patient Care

AUGUSTUS S. ROSE, MD

The editors are to be commended for opening discussion on "Orthodox Medicine, Humanistic Medicine and Holistic Health Care." The articles in the December 1979 issue and the responding forum statements are interesting and informative. They provide physicians who are genuinely concerned with the best in patient care a broadening of perspectives, and an opportunity to understand how others think about the complex and sometimes controversial ideas extant in modern health care. Being of a comparable "vintage" and with a similar orientation, I am particularly attracted to the statements "Care of the Patient" by Louis K. Diamond, MD and "A Balance of Science and Art" by Dwight L. Wilbur, MD, which appeared in the January issue. Orthodox medicine when viewed with the interpretation of these men surely has no reason to feel challenged by the trends in health care as proposed by humanistic medicine and holistic health care. *Good* physicians who seek to practice the art of medicine incorporate most, if not all, of the principles involved.

The art of medicine, revered in concept and recognized as a strong, beneficial influence in patient care, has never found a place in the curricula of medical education. It is said that the art of medicine cannot be defined with accuracy, cannot be measured objectively and cannot be taught except by example. In general, the art of medicine is *explained* as a professional and personal attribute that is acquired by only a few physicians. In the context of the discussions concerning modern medical practice, it is suggested that young physicians who seek to gain a comprehensive approach to patient care can with motivation acquire many of the skills and attributes that fall into the category of the art of medicine. Yet, because of the reasonable and appropriate influence of scientific medicine the present-day physician should have justification and understanding about how certain personal and professional qualities in practice become effective in the therapeutic process.

As pointed out by several writers in this series, modern medicine, which had its origin in close association with religion and religious beliefs, still retains, despite the advances of scientific medicine, a basic relationship that is in the realm of the spiritual. Those who are ill, without knowledge and often in desperation, look to *higher powers* as well as to those who are credited with knowledge and experience. In this sense and regardless of how this attitude may be camouflaged in modern times, the one who in distress turns to the physician for help is a *supplicant*—admitting dependence and acknowledging readiness for information and desire for help. This places the physician in an advantageous position and almost regardless of the nature of the therapies or ministrations, if thoughtfully and confidently prescribed, a degree of comfort and benefit will result. It is within this concept that various systems and therapies, both those with and those without a scientific basis, appear to gain the first measure of success. Excepting the specifics in metabolic and nutritional deficiencies, certain infections and the like, and the exquisite skills of modern surgery, success in medical practice depends in large part on how a therapist develops

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and utilizes the confidence that is engendered in the patient.

Medicine and medical science have been prone to explain these circumstances by citing a placebo effect. But as has now been shown,[1] at least in the area of pain research, a placebo when administered confidently and authoritatively will in many instances generate the production of peptides within the central nervous system which activate opiate receptors and bring pain suppression. These effects and those of other therapies, therefore, can be understood as resulting from the activation of native physiological mechanisms within the nervous system. And, since the nervous system—mind and emotions—not only regulates behavior in relationships to the outside world but also has strong and directive influence over internal bodily functions, a therapist who provides the patient with information and administers appropriate methods of treatment takes advantage of innate physiology that has the capability to assist in recovery from tissue injury and disease and in making adjustments to disability.

It behooves practicing physicians to strive toward understanding the total life situation of each patient and to thoughtfully gain the patient's confidence and encourage belief in the modes of therapy while also utilizing up-to-date knowledge in patient care.

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Holism and Socioeconomic Reality

STEPHEN R. LEMKIN, MD

THE MOUNTAIN OF VERBIAGE about "holistic" medicine in recent issues of the journal misses the point, I think, almost entirely. The yearning of our patients for the holistic approach is symptomatic of a general discomfiture with current socioeconomic reality rather than a symptom of a dying medical care system.

One of the reasons for the triumph of orthodox medicine over competing systems in the early part of this century was that orthodox medicine at the time was essentially holistic. Much of medical care centered on the family doctor who made his often meager living by attending to overall emotional, social and medical needs of patients he knew rather intimately. I remember my family *doc* coming to the house when I was a child to treat some minor illness in the family, usually without any specific or sophisticated therapy, following which he would sit over a cup of tea discussing current family and neighborhood crises and offer his wisdom. As he left, my mother would force him to take two or three dollars. This, I submit, is essentially the concept of holistic medicine shed of its pretentiousness and pseudosophistication. Remember, though, in those years we also had a "holistic" milkman, a "holistic" grocer and so on.

In the last 20 years medicine and *all other service institutions* of American society have evolved away from this wistfully remembered state for basically socioeconomic reasons. The truth is that there are no family docs like that any more and no milkmen like that any more. As has been pointed out by others, the postwar years have provided an explosion of relative wealth, despite inflation, to most members of the middle class, and we have come to expect it. With the proliferation of medical technology at the same time, a lucrative industry has developed which focuses on the use of such technology and which has naturally generated the system of expensive medical specialization most of us emulate and participate in. The result is, I think, that the average physician now is relatively wealthier than his predecessor and he is without the economic *need* to provide old-fashioned "holistic" care. The same is true of the corner supermarket and the corner plumber.

The real danger is that those who decry this social change, whether for altruistic reasons or not, would like to focus on Medicine as the villain, rather than our postwar socioeconomic environment as a whole. This is easy and tempting to do because we practicing physicians are visibly affluent, the medical care we provide is painfully and burdensomely expensive, and yet we are somehow expected to conform to a set of standards harking back to simpler days.

For idealists who believe in the return to the holistic, unfragmented, personal approach to medical care, there is a real economic dilemma. A friend of mine, fully trained in internal medicine, opened a practice for holistic care more than

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a year ago. He tries to focus on the total patient, with the aid of several techniques such as biofeedback, relaxation training and much personal attention, in addition to orthodox internal medicine. Because of the time required to provide this kind of care up to his own personal standards and his lack of expensive gimmicks, he is still struggling to meet his monthly overhead. I know of no *conventional* internist who is having the same problem.

In the future, of course, we will see holistic "factories" and a further proliferation of minimally trained paraprofessionals who want a piece of the action. If society wants a return to holistic practice, it must be willing to pay for it, and I do not think it is. If the inexorable proliferation of HMO's is an indication of the future of medicine, and it certainly appears to be, we will be seeing less personal attention for patients, not more. It is within this environment that our patients can be easily seduced by facile promises of a "new order."

Teaching the Psychiatric Aspects of Medical Practice and the Psychosocial Factors in Healing

DAVID H. ROSEN, MD

I WANT TO COMMEND the editors of THE WESTERN JOURNAL OF MEDICINE for publishing the excellent series of articles in the December 1979 issue on "Orthodox Medicine, Humanistic Medicine and Holistic Health Care," and for providing a forum for continued dialogue and discussion. I want to share with the readers information concerning an innovative educational program, "The Psychiatric Aspects of Medical Practice" at the University of California, San Francisco (UCSF), that attempts to integrate orthodox and humanistic medicine and emphasizes a holistic approach towards patients as suggested by Tupin.[1] This new course seeks to help future physicians restore the balance between the art and science of medicine[2] and to maintain the other vital balance between medical proficiency and knowledge of oneself.[3,4] It focuses on caring for the patient and healing the whole person in addition to attending to the patient's disease.[5,6] The course also represents a working example of Engel's "biopsychosocial model," which he has proposed as a needed alternative to the classical "biomedical model."[7]

The Psychiatric Aspects of Medical Practice course is a weekly two-hour clinical seminar that operates as an integral part of the following required core clerkships: Medicine, Surgery, Pediatrics, Obstetrics and Gynecology, Neurology, and Ambulatory and Community Medicine. Students master a body of knowledge[8] and present their own patients to the psychiatric faculty in a case conference format. The faculty member interviews the patient and leads a discussion that might cover any or all of the following: (1) psychological factors or life stresses related to the onset of the patient's illness, (2) coping with the stress of illness and hospital stays, (3) psychosocial sequelae of an acute, chronic or terminal illness, (4) the patient's understanding and meaning of his or her illness, (5) the healing process —the effective doctor-patient relationship, (6) psychiatric conditions that manifest in a medical setting (most commonly depression) and (7) possible therapeutic interventions related to any of the above with follow-up in subsequent seminars.

The idea for the Psychiatric Aspects of Medical Practice course originated with a medical student on the UCSF Curriculum Committee. In response to the Department of Psychiatry's request for more clerkship time, this student suggested that psychiatry be taught in a relevant and practical way as part of the other core clerkships because the majority of students were going into family medicine and primary care areas. The Curriculum Committee supported this student's idea and in early 1977 the course was successfully piloted on the Medicine core clerkship.[9] Intensive independent evaluation showed that students who participated in the pilot seminar increased their knowledge of psychosocial concepts in medical care, showed evidence of more empathy and sensitivity, and maintained a strong belief in having the patient share in the responsibility of his or her care. Students who were not in the pilot group were significantly less empathic and sensitive and showed significantly less will-

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ingness to involve the patient in the care. The same results were obtained from thorough pre-evaluations and postevaluations as the course was expanded in 1977-78 to all six clerkships at Moffitt Hospital.

In July 1978 a grant from the Henry J. Kaiser Family Foundation (Palo Alto, California) enabled the Psychiatric Aspects of Medical Practice program to fully expand to all affiliated hospitals. We now have 22 sections of the course operating year-round. Our faculty has grown to 40 and includes some other medical specialists who teach with our psychiatric faculty. This is ideal and we would like to see more of this in the future.

Students have responded very positively to our course and at present 80 percent of the sections are rated above average. Of course, it is the personal reactions and comments that capture the essence of the course. A student recently characterized the course as "An isle of humanity in a sea of technological medicine."

I agree with Joe Tupin that the key task is integrating orthodox and humanistic medicine and that this is the challenge of the 1980's. In order to focus attention on this critical need, we are sponsoring (again with the support of the Henry J. Kaiser Foundation) a National Conference on Teaching the Psychiatric Aspects of Medical Practice and the Psychosocial Factors in Healing. This conference will be held May 4, 1980, at UCSF and medical and psychiatric educators are being invited to attend from all the medical schools in the United States. Speakers include George Engel, Robert Glaser and Norman Cousins. Faculty and students from the Psychiatric Aspects of Medical Practice program will also be involved in the conference.

It is to be hoped that the Psychiatric Aspects of Medical Practice program and the National Conference are part of a growing effort by our profession to meet the current challenge to modern medicine.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Planning for Health Manpower

To the Editor: As director of the state agency responsible for health manpower planning in California, I was pleased to see the November 1979 editorial on the subject.

I concur with statements in the editorial that health manpower planning is a complex subject. I agree that it is neither prudent nor necessary to attempt long-term, precise health manpower planning. Certainly, it is not desirable to conduct such planning without consideration of the real-world limitations. The Office of Statewide Health Planning and Development is fortunate to have health manpower *development,* as well as health manpower *planning,* responsibilities. Through such programs in California as the Song-Brown Family Physician program, the Health Manpower Pilot Projects program, the Allied Health Occupations Project, and our involvement in the planning for the Statewide Area Health Education Centers, we become part of an interdependent network. Our biennial Health Manpower Plan, therefore, is an action plan and in it we note the hazards of attempting to fine tune the health manpower system.

I appreciate your analogy, comparing a health manpower plan to a medical treatment plan. As health planners, the community (the state) is our patient. We sense that there is an illness in the body politic, an illness characterized by a surplus of health care resources in some localities and a scarcity in others, a lack of adequate access to health care for many members of the body politic, an inefficient use of health personnel resources, and an orientation of the system toward sickness rather than health. In spite of vast public and private expenditures on this patient, there is little evidence of improvement. Our part of the medical system, to continue with your analogy, is to develop health manpower planning processes sensitive to community need.

The editorial mentions the ingredients that constitute health manpower planning: the population and demographics of the areas involved, services needed, types and numbers of health personnel resources required, and so forth. The editorial accurately acknowledges that none of these is static. I would also add that health manpower planning is not static, either. Through the planning activities mentioned above, we continue to gain new knowledge and sensitivity. We have matured in our recognition of the environment and setting in which our efforts take place, the limitations of our activities, and their interaction with others. But we have also grown in the recognition that our efforts are not futile, and that we are having an impact on the health manpower scene.

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One More Hazard

To the Editor: Kudos to The Western Journal of Medicine for the January 1980 Epitomes of Progress—Pediatrics, which dealt in large part with pediatric hazards. May we add one more hazard that is sometimes overlooked?

Carrageenan, a sulfated polysaccharide derived from red seaweed, is added to many products to stabilize suspensions of milk protein. At present it is added to all infant formulas fed to premature infants in the United States. Although carrageenan was shown to be safe when fed to normal full-term baboons,[1] studies done on rabbits and guinea pigs[2,3] have shown that it produces mucosal ulcers in the cecum and proximal colon of these sensitive, herbivorous laboratory animals. Moreover, since necrotizing enterocolitis occurring predominately in premature infants is characterized by necrosis of the developing gastrointestinal tract,

it has been suggested[4] that there may be a relationship between carrageenan ingestion and this malady.

We therefore believe carrageenan should not be fed to developing premature infants (some of whom may be uniquely sensitive) until data prove it does not cause the mucosal changes it causes in laboratory animals. Human milk, of course, contains no carrageenan and is preferable.

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Of Technology and Accountability

To THE EDITOR: The 70's are behind us, and what have we accomplished?

A "test tube baby" was conceived and born, and lives today. Computers entered the field of medicine as both a threat and a blessing. Radioactive isotopes now enable us to scan our body's anatomy, and to evaluate organ functioning. Computerized axial tomography, working like a huge, painless microtome, can serve up slices of our brain and body for diagnostic study.

Fetal monitoring came to the obstetric wing and advanced perinatal care now permits the survival of premature babies weighing as little as 1,500 grams. Operative delivery rates soared.

Beta blockers were finally allowed to fly across to our shores, as was that magic medicine for peptic ulceration, cimetidine. It seemed we were regularly presented with a new "antimicrobial-of-the-month."

To the delight of orthopedic surgeons, and to their patients suffering from destructive arthritis, a nonreactive glue was synthesized and joint replacement was on its merry way.

Surely, the 70's deserve to be called the Golden Decade of Technology, an exciting ten years of scientific achievement.

And yet, ironic as it may seem, every physician has an ache in his heart knowing that along with these giant strides in technology we have sustained shocking blows to our collective pride. Our profession, long accustomed to high marks in credibility, began, during these ten years, to be made painfully aware of the requirement to prove our competency in caring for patients and to demonstrate our *accountability*.

The Age of Technology was also the Age of Accountability. No longer is it enough to say that the personal drive in every physician is adequate motivation for the maintenance of competence. No longer does it suffice to point out that we patrol our own ranks, that we mull over our failures in clinicopathologic conferences (CPC's) and in death conferences, and that we all have stern-faced tissue committees constantly looking over our shoulders.

Now we are to have formalized Peer Review, state and national Professional Standards Review Organizations (PSRO's) and a required number of medical audits. Compulsory continuing medical education (CME) is to be a prerequisite for medical organization membership, special recertification, staff membership—even for relicensure. Gone are the days of voluntary maintenance of competence. Thanks to the 70's we are being held *accountable*.

How did it happen? Consumerism, as it swept across our nation, must get some of the credit. The malpractice "crisis" of 1974-75, whether manufactured or real, gave the media, the underwriters and, of course, the public the right to demand professional accountability. And we had to learn that when the government and other third parties collect and distribute the monies to pay for medical care, they can rightfully demand that they get what they pay for. It is an unavoidable demand for more accountability.

Our profession appears to be entering the 80's determined to roll with the punches. We seem ready to tell everyone that we intend to be accountable, just as we always have been in the past. We will vote the voluntary, rather than the compulsory, ticket: voluntary CME, voluntary self-assessment, voluntary practice-analysis.

Technology will surely continue its forward strides during the 80's, and our profession will continue to proclaim staunchly that we physicians are accountable. But let the proof of our accountability come not through outside regulatory agencies but from within our own ranks.

E. R. W. FOX, MD
Special Editor for Idaho
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Health Care in China

To the Editor: I find it ironic that the article "Health Care in China—An Individual Responsibility" appeared in the December issue under the rubric of "Informed Opinion." It might better have been labeled "Uninformed Opinion" or "Totally Uncritical Sycophancy." I hope you will endeavor to balance this lopsided view of the alleged triumphs of health care in Communist China under Mao Tse Tung with a more objective report in the future.

We are told that after efforts begun in 1965 "the health status of a quarter of the world's population appears to have improved substantially and dramatically within the past few years." The references cited are dated from 1973 to 1976, so that at the very outside, these remarkable changes took place over an 11-year span. Further, "the life span has increased from 40 to 70 years; infant mortality levels now rank among the lowest in the world; undernutrition, venereal disease, drug addicition and several of the most devastating epidemic diseases have been virtually wiped out. . . ."

Particularly intriguing to me is the feat of compacting time so as to measure a 30-year increase in longevity in a 10-year period (all the more impressive because with the Cultural Revolution the number of people clubbed to death by the Red Guards would be expected to have a serious adverse effect on longevity increases achieved through improved health care).

Oh yes! The flies were all eradicated by the Communists long before the Cultural Revolution. Why did it take so much longer to eliminate venereal disease, drug addiction, undernutrition and poverty (the soil that nurtures so much human disease, as anyone trained in public health knows)?

I find that some otherwise erudite and sophisticated medical colleagues will swallow whole any contrived data and showcase studies emanating from totalitarian countries, and the more preposterous the claims, the less critically they pass into the decerebrate central nervous system, there to be regrouped and articulated in printed form, and published in a learned tome.

THAYER A. SMITH, MD
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Creased Earlobe Syndrome: A New Wrinkle?

To the Editor: The creased earlobe syndrome and its possible relation to hypertension as a pathognomonic sign have been of interest to the medical profession for a number of years. The article by Nicholas L. Petrakis in the January 1980 issue of the journal is very interesting and well written.

I have creased earlobes, and have had known hypertension for the past six years, though asymptomatic. I am on a regimen of antihypertensive medications. I also had three back operations 20 years ago, and since then have been unable to sleep comfortably in the supine position. Because I am much more comfortable on my left side, I sleep at least 80 percent on this side. I have two deep diagonal creases on my left earlobe, but only one rather shallow crease on my right. I have noted this for many years, and am also aware that when I do sleep in the side-lying position, my earlobe, which is rather large, is invariably folded over. I likewise have many more creases beneath my left eye than I do under my right one.

Before the creased earlobe syndrome gets into the medical dictionary as being pathognomonic of heart disease, perhaps someone should make a study of earlobes of people with chronic back problems. Maybe this will eventually turn out to be the "oh my aching back" sign.

C. ARTHUR SPAULDING, JR., MD
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Refer to: Andrews NC: Continuing medical education tuition: A survey of charges (Medical Education). West J Med 132:368-378, Apr 1980

Continuing Medical Education Tuition: A Survey of Charges

NEIL C. ANDREWS, MD, *Davis, California*

A survey was carried out on the tuition charged for continuing medical education (CME) programs offered by a variety of providers. These included schools of medicine throughout the United States, national organizations and societies, state-wide organizations and societies located in California, and a small group of hospitals in or near Sacramento, California.

The fees charged for continuing medical education (expressed in this article as the amount in dollars that a physician must pay for one hour of approved Category I credit) may vary from nothing to more than $20 an hour. The average charge per hour for CME courses sponsored by medical colleges in the United States ranged from none to $11.19 during 1976 and 1977. Recent data indicate that most schools have increased tuition for CME courses because of inflation. Many schools of medicine provide CME through grand rounds, conferences and special lectures at no cost to participants. Similarly, in a small sample of hospitals in California, CME was found to be available at a minimal charge to physicians.

Some CME programs are more costly because fees may include the expenses of honored visiting faculty, and costs of food or social activities. There may be further expense if travel is required, although these additional costs may be offset by the benefits of study in a relaxed atmosphere away from practice and office pressures.

THE TUITION CHARGED for continuing medical education (CME) has become a concern of physicians, particularly those practicing in states that require CME as a condition for relicensure or for those who are members of professional organizations or societies that have made this a condition for membership.

Oetting[1] in 1978 stated that the then current rate of tuition for Category I CME programs presented by the American Medical Association (AMA) for its own membership was $10 per clock hour. Lockard[2] reported a six-year study by the American Society of Clinical Pathologists of which the most recent survey was conducted between July 1, 1977, and July 1, 1978. Using data gathered from 553 continuing education programs sponsored by 45 organizations and societies, he concluded that national medical societies or organizations had an average per-member charge for each hour of CME of $12.72, with a range of $7.69 to $20.00. Thirty-seven medical schools, graduate schools and hospitals had an average cost for each CME hour of $10.04, with a range of $2.50 to $21.25. Ten commercial, governmental, private and nonmedical organizations had an average cost per CME hour of $16.25, with a range of $2.86 to $50.00. Some 496 societies and organizations that presented large multiple programs had an average member cost per CME hour of $12.26, with a range of $3.81 to $20.65. He concluded that the overall average charge per

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hour for continuing education was $12.18, with a range from $2.50 to $50.00.

Miller[3] has estimated that approximately $3,616,770,000 is spent for continuing medical education annually. He arrived at this figure by estimating the out-of-pocket expense of physicians and the expenditures by hospitals, medical schools, medical associations, industry and government, together with the loss of income from patient care. To these he added an estimated additional cost for inflation and took into account the increase in the number of physicians practicing in the United States.

In California, physicians' concern about tuition for CME programs, particularly that charged by medical schools, became evident during the 1977 annual meeting of the California Medical Association (CMA), and resulted in the following resolution being presented to CMA's House of Delegates:

> Be it resolved that the Committee on Continuing Medical Education be instructed to promptly devise and report to the California Medical Association Council a plan for insuring that approved continuing medical education courses will be offered at fees and charges which are firmly tied to the budgeted cost of presenting each program.

When this resolution was discussed by the Committee on Continuing Medical Education of the CMA, the members who represented the several medical schools stated that this resolution was unworkable. The reasons given were that most departments or units responsible for continuing medical education in the medical schools in California did attempt to relate tuition for a CME program to the expenses incurred during the development of the program. However, because six of these departments received no financial support from their parent institutions and two received only minimal support, fiscal responsibility required that all costs incurred in the development and presentation of CME programs during any one academic year must be paid by income from tuition, donations and other sources during that year. Some CME programs are financially successful, others are not. The successful programs must of necessity support the less successful ones. A simple solution would be to eliminate the unuccessful programs and offer only those that were known by past experience to be popular, well attended and, therefore, financially sound. This solution was unacceptable because some of the less well-attended programs were designed to present recent advances or review material that had been identified as important subjects for practicing physicians. Other unsuccessful programs failed because of competition from national meetings or regional programs that were directed to the same audience. The CME Committee of the California Medical Association recommended that a survey of tuition and fees charged by other medical schools and other organizations sponsoring CME programs be undertaken to determine whether the fees charged in California were excessive compared with other CME providers, and to establish a data base regarding charges for CME in California and the United States.

The California Medical Association requested an answer regarding tuition and fees from the committee by late 1977. To obtain preliminary data a survey was done of CME programs presented by the eight schools of medicine in California and eight hospitals located in or near Sacramento that were accredited to give Category I credit by the CMA between January 1, 1976 and June 30, 1977.

The preliminary findings presented to the California Medical Association in 1977, are included in this report.

Methods

A questionnaire was developed to be sent to schools of medicine with known programs in continuing medical education (Figure 1). It was mailed to 80 medical schools throughout the United States, with a covering letter requesting that the questionnaire be completed and returned. Each school also was asked to include copies of all available brochures for programs presented between January 1, 1976, and June 30, 1977. The questionnaire was sent, in addition, to several national societies and organizations, and a modified questionnaire was sent to a number of California societies, organizations and hospitals accredited by the California Medical Association.

Brochures about CME programs given during the survey period were collected from many American Medical Association accredited sponsors of CME and used to supplement data not available from other sources. Only material concerning Category I CME credit was included.

Each respondent was asked to report the range of tuition charged for programs offered during the period of the study as well as the range of tuition per clock hour for these CME programs. The latter was to be determined by dividing the

course tuition by to the total number of Category I hours that could be earned by each person attending. The fee per hour for acceptable credit was chosen as the unit which could best provide a comparison of charges for programs within each institution and for CME programs offered by other schools, societies, organizations and hospitals.

Analysis of fees for a CME program does not indicate or measure the quality of the educational experience that might be obtained by those attending that course. This determination must be made by each potential attendee based on his needs, and his knowledge of the sponsor and faculty chosen to present the program.

Results

Of the 80 medical schools, 55 (69 percent) responded to the questionnaire. Of these, 32 returned the questionnaire and 23 completed the questionnaire and supplied brochures as well.

1. How many continuing medical education programs did your department sponsor between January 1, 1976 and June 30, 1977? _____

2. What was the highest tuition charged for these programs? $_____

   What was the lowest tuition charged for these programs? $_____

3. In order to determine the average tuition charged by your department please divide the total tuition costs of all programs by the total number of Category I credit hours offered.

   Average cost per hour for continuing medical education $_____

4. Is there evidence that your costs for continuing medical education programs are increasing, i.e., is the tuition between the period January 1, 1976 to June 30, 1976 the same ____, lower ____, or higher ____ than during the period January 1, 1977 to June 30, 1977?

5. What are the identifiable reasons for the higher costs of these programs?

   a) Program requires special effort such as specific locations _____, dissecting material _____, instruments _____, etc., explain _____ _____.

   b) Tuition includes supplying educational materials such as books _____, Manuals _____, reference material _____, etc., explain _____ _____.

   c) Tuition includes meals ____ yes, _____ no. Housing ____yes, ____ no.

   d) Special and/or expensive speakers required ____yes, ____no.

   e) Other (specify) _____ _____ _____

6. Does your Department of continuing Medical Education receive support from your parent organization, i.e., Medical School? ____yes, ____no.

7. What percentage of the cost of your program is contributed by your school? ____%

8. What percentage of the cost of your program is received from drug houses or other sources? _____%

9. What percentage of the costs of your program is from tuition? _____%

10. May I use the name of your School in the document which will report the results of this survey? ____yes, ____no.

Figure 1.—Questionnaire concerning tuition for continuing medical education programs.

The 55 medical schools have been divided into the four geographic regions used by the American Association of Medical Colleges and designated Northeast, Midwest, South-Southwest and West. Each school has been assigned an identification number which has been used throughout the report and in the tables and figures. Responses were received from 16 institutions in the Northeast and 13 each from the Midwest, South-Southwest and West.

Table 1 indicates the number of programs offered by the 16 medical schools located in the Northeast region of the United States. The range of tuition per course, and per hour when available, and the average tuition per hour of all CME programs offered have been tabulated. Six of the 16 schools offered some courses for which no tuition was charged. The average regional tuition (the sum of the average tuition of each school divided by the number of schools) was $8.06.

Table 2 gives the same information for the 13 schools located in the Midwest. Six schools responded that they presented some CME programs without charge. One school did not complete a portion of the questionnaire because that school had not been accredited. The average regional cost was $6.68.

Table 3 presents the data for the South-Southwest schools. Three schools sponsored some programs for which no tuition was charged. School 39 did not include data that allowed calculation of the average tuition per hour for its programs. The average regional cost was $6.36.

Table 4 summarizes the data from the 13 schools in the Western area collected during both the pilot and subsequent surveys. Only one school in the Western area presented some formal CME programs without tuition. The average regional cost was $7.09.

Although only one of the eight California schools presented formal CME programs without tuition, it was found on further investigation that each school offered a large number of hours of Category I credit for which there was no charge. These included grand rounds, tumor conferences, special lectures by invited guests and other educational sessions. These were open to practicing physicians on a place-available basis. The number of hours offered by each of the eight schools in California in 1978 is shown in Table 5.

One aspect of the study of tuition was to determine how many of the schools that developed CME programs received support from their parent

TABLE 1.—*CME Programs Offered in the Northeastern Area, 1976-1977*

Medical School	*Number of Programs*	*Range of Tuition per Course*	*Range of Tuition per Hour*	*Average Tuition per Hour*
1	52	$ 0- 150	$ 0-10.00	$ 6.97
2	30	15- 80		8.00
3	21	45- 350		9.00
4	96	25-1300		9.15
5	35	0- 650		4.75
6	123	45- 850	5.63-13.16	9.00
7	65	0- 500		8.32
8	121	45- 648	8.00-18.00	10.80
9	7	0- 400		9.00
10	83	5- 800	0.71-44.44	11.19
11	5	20- 175	6.73-10.00	9.36
12	50	5- 150		8.00
13	33	20- 500	2.00-13.93	7.55
14	NA	0- 380		6.25
15	54	15- 250		5.41
16	64	0- 475		6.25

CME=Continuing Medical Education
NA=not available

TABLE 2.—*CME Programs Offered in the Midwestern Area, 1976-1977*

Medical School	*Number of Programs*	*Range of Tuition per Course*	*Range of Tuition per Hour*	*Average Tuition per Hour*
17	150	$ 3-160	$7.00-10.00	$ 8.50
18	216	5-200		7.00
19	34	0-200	0-13.33	6.04
20	45	140-250	5.38- 7.46	5.90
21	16	0-340	0- 9.29	6.09
22	127	0-475		4.45
23	20	15-315	2.00-22.92	9.72
24	37	0-250		8.00
25	11	0-100		Not Accredited
26	23	7-300		4.33
27	40	0-350	0-16.67	5.25
28	22	25-120	2.78-12.00	8.41
29	5	40- 75	5.00- 8.33	6.57

CME=Continuing Medical Education

TABLE 3.—*CME Programs Offered in the South and Southwestern Area, 1976-1977*

Medical School	*Number of Programs*	*Range of Tuition per Course*	*Range of Tuition per Hour*	*Average Tuition per Hour*
30	17	$ 5- 75	$0.71-12.50	$ 5.20
31	3	10- 50	2.00- 6.67	4.97
32	45	10-150		4.00
33	360	20-235		8.00
34	24	25-295	1.00-20.00	6.92
35	24	10-250		7.32
36	45	50-500	1.71-18.00	9.66
37	27	0-225		5.25
38	83	5-175		5.00
39	29	50-250		NA
40	24	65-150		7.50
41	38	0-225	0-18.75	5.35
42	30	0-200		7.13

CME=Continuing Medical Education
NA=not available

TABLE 4.—*CME Programs Offered in the Western Area, 1976-1977*

Medical School	Number of Programs	Range of Tuition per Course	Range of Tuition per Hour	Average Tuition per Hour
43	9	$ 75-200	$4.69-15.00	$ 7.68
44	69	0-225		5.11
45	6	25-230		9.50
46*.....	22	25-150	4.69- 6.67	6.12
47	78	50-250	4.30-12.22	7.06
48*.....	22	35-275	6.36-12.50	9.80
49	32	50-150	6.36-10.00	8.44
50*.....	19	25-425	2.00-14.10	5.43
51*.....	13	20-300	2.88-13.80	7.53
52*.....	35	40-360	2.75-20.45	10.47
53*.....	13	12-375	2.00-23.44	8.97
54*.....	30	20-250	4.00-15.00	7.18
55*.....	49	11.50-350	3.57-17.86	9.43

CME = Continuing Medical Education

*Schools in California included in the preliminary study.

TABLE 5.—*Grand Rounds and Other Tuition-Free Accredited Teaching Activities, 1978*

Schools of Medicine, California	Number of Hours per Year
Loma Linda University	1,664
Stanford University	6,100
University of California, Los Angeles	1,000
University of California, Davis	2,345
University of California, Irvine	1,995
University of California, San Diego	1,826
University of California, San Francisco	2,250
University of Southern California	3,060

institutions. Figures 2 through 5 present this information for the 55 schools in the four regions that responded to the questionnaire. The solid bar on the left indicates the average charge for tuition per hour of CME for each school. The adjacent bar represents the source of the support for CME. Thirty-five (64 percent) medical schools reported that they received some support for their CME activities from their parent institutions. The amount of this support varied widely, ranging from 0.4 percent to 95 percent. School 39, which did not indicate its average cost per hour for CME, replied that the medical school totally supported its CME programs. This response has not been included in Figure 3 because it is unlikely that tuition does not represent some portion of that school's CME budget.

In the Northeastern, Midwestern and South-Southwestern areas of the United States, approximately 69 percent of the schools received some support for their CME activities. In contrast, only 14 percent of the schools in the West received support and none received more than 25 percent of the total CME budget from their parent institutions. In California, two private schools had 15 percent of their CME activities supported by the parent institutions.

A second consideration regarding medical

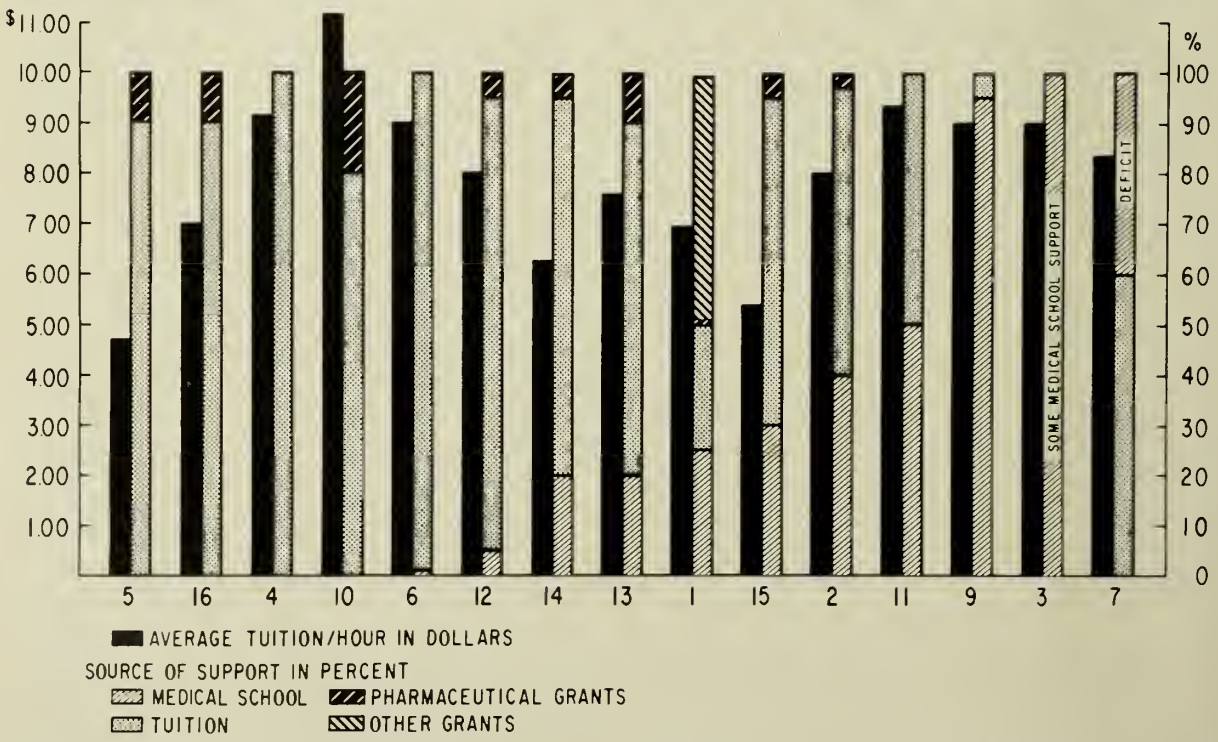

Figure 2.—Relationship between average tuition of continuing medical education per hour and source of support of program—Northwest region.

school support of CME programs was to analyze whether that support resulted in a reduction in tuition charged to those attending. The data show that 30 of the schools surveyed charged a tuition that was the same as or higher than the regional average. Of these, 15 received financial support in amounts ranging from 5 percent to 95 percent of their total annual expenditures. Seven schools received less than 25 percent and seven received more than 30 percent of their income from their parent institutions.

In contrast, 20 schools presented programs

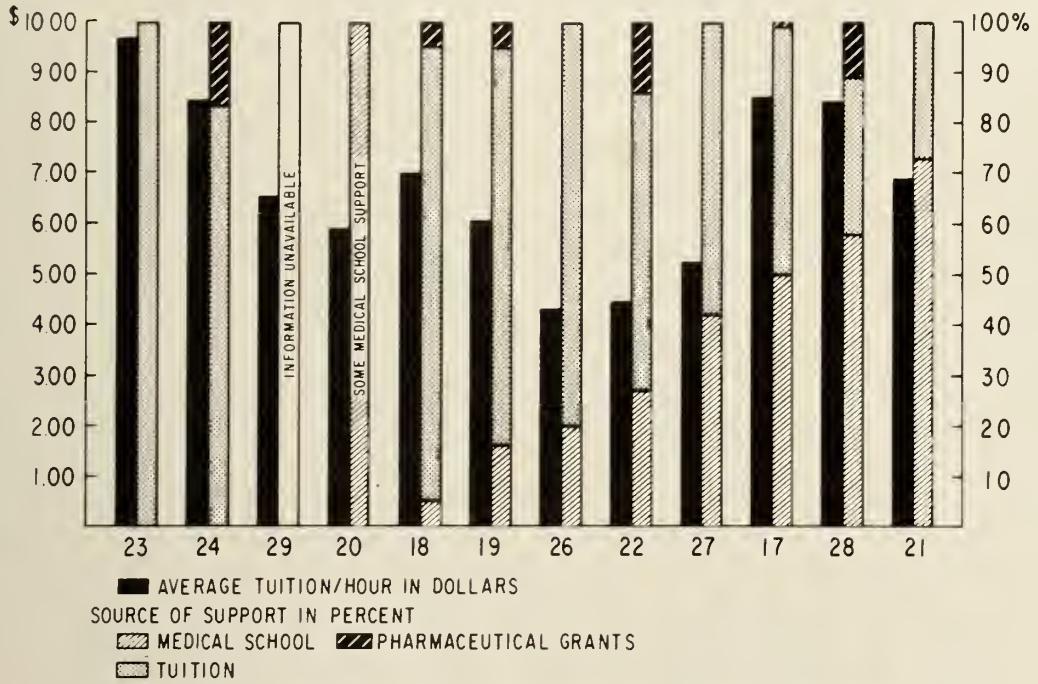

Figure 3.—Relationship between average tuition of continuing medical education per hour and source of support of program—Midwest region.

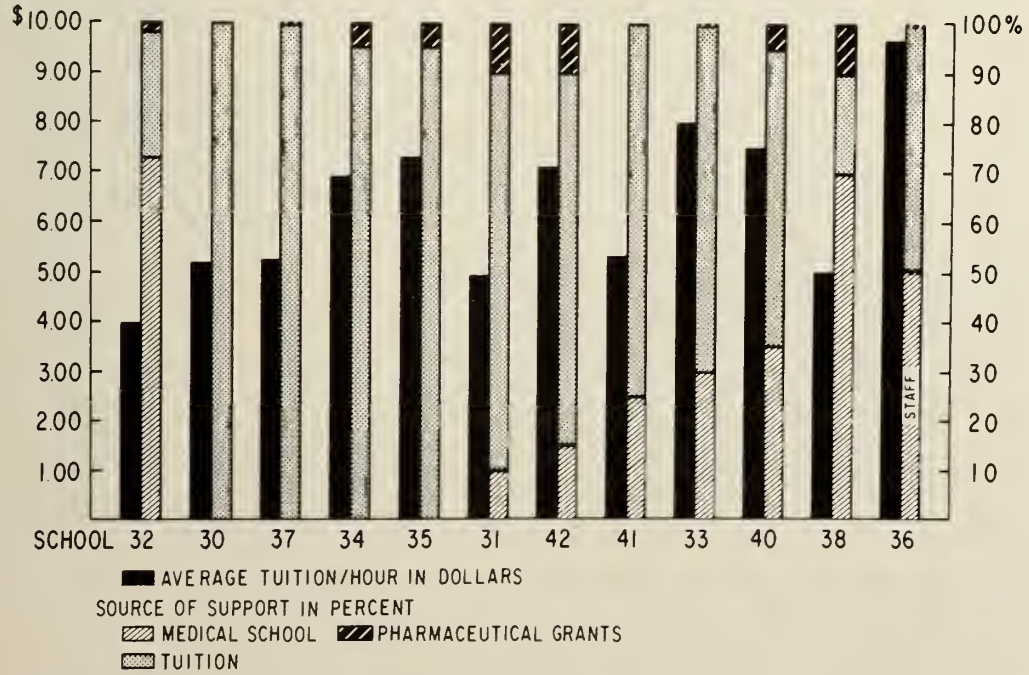

Figure 4.—Relationship between average tuition of continuing medical education per hour and source of support of program—South and Southwest region.

that had tuition charges of less than the regional average. Fifteen of these received support ranging from 5 percent to 73 percent of their expenditures. Seven schools received less than 20 percent and eight received between 25 percent and 73 percent of their annual expenditures.

Information regarding medical school support of CME activities was not supplied by four institutions, and one indicated that the CME department received "some" support from its parent institution.

An effort was made to determine why some programs of comparable length had a higher tuition per hour than others in the same institution and in institutions within the same area. The brochures submitted by the medical schools were reviewed to determine the reasons for these variations. Differences in tuition appeared to be related to the proportion of local versus visiting faculty participating in the program and the inclusion in the tuition fee of the cost of coffee breaks, meals and social activities. Banquets and lodging were rarely included in the tuition charged.

To determine the cost of an hour of CME in the eight Sacramento hospitals each hospital was asked to provide information regarding annual expenditures for such items as the salaries of the Director of Medical Education and his secretary; the honoraria, travel and other expenses paid to faculty; the cost of educational materials, space, advertising and notification of staff, and any other identifiable costs. Although this information was not supplied in as much detail as requested, sufficient data were provided to develop Table 6. Of interest is the relatively small charges made to physicians attending these CME programs.

This sample of eight hospitals in a state that has 584 hospitals is, obviously, preliminary; a subsequent and more extensive study has been initiated to accurately establish the cost of CME in the 290 hospitals accredited by the California Medical Association.

Charges for CME programs sponsored by California organizations and societies are given in Table 7. As can be seen, of the 18 societies responding, most of the costs of CME activities were paid from membership dues. Only two charged tuition and a few obtained grants from either foundations or pharmaceutical companies to assist in supporting their CME activities. Some support of CME activities came from donations by staff members' wives and the sale of exhibit space.

The California Medical Association has not been included in Table 7. This association annu-

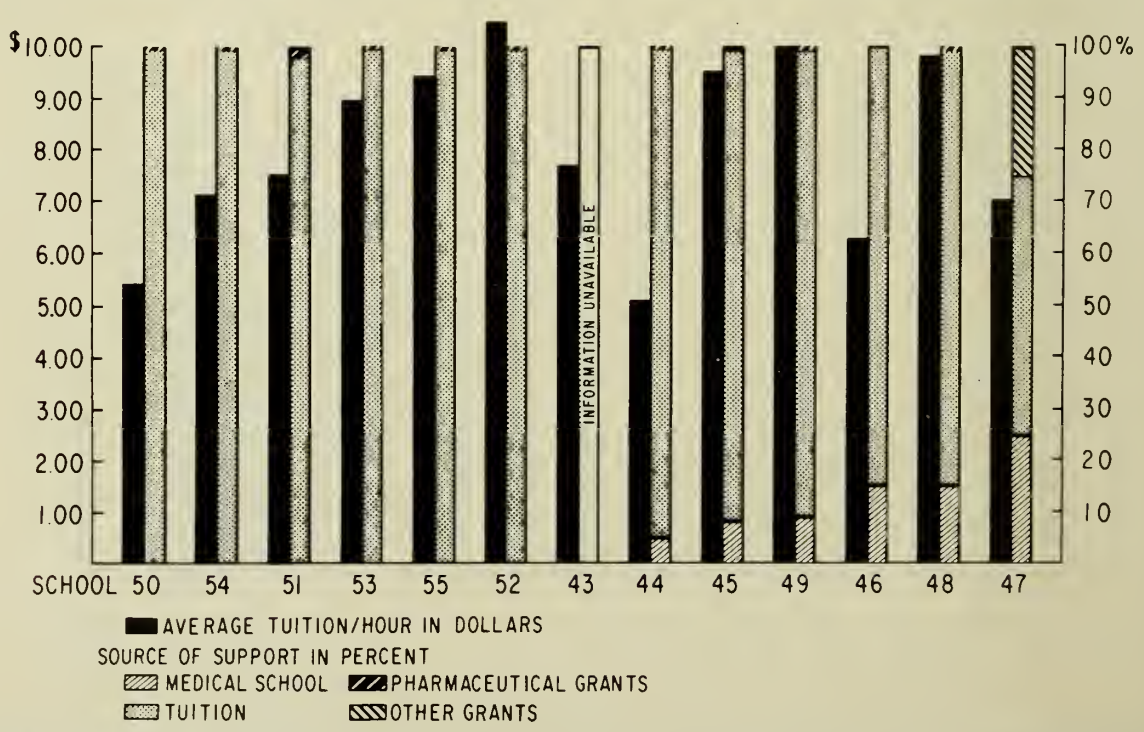

Figure 5.—Relationship between average tuition of continuing medical education per hour and source of support of program—Western region.

ally co-sponsors two or three Postgraduate Institutes with each of the California schools of medicine. Most programs offer between 10 and 13 hours of credit with a total tuition of $60 for members and $90 for nonmembers. The tuition per hour ranges from $4.61 to $6.00 for members and $7.50 to $9.00 for nonmembers. The income from tuition for these Postgraduate Institutes pays for the honoraria and travel expenses of speakers, brochure development and mailing, staff costs during the program, and a small donation to the cooperating school of medicine. All other costs for development of the Postgraduate Institutes are absorbed by CMA. This subsidization of programs permits a relatively low tuition for practicing physicians and allows retired physicians to attend the Institutes without paying any tuition.

A survey of tuition charged by national organizations for CME programs is presented in Table 8. The data were supplied through the courtesy of the Executive Director of the American Academy of Dermatology. The charge per hour for members and nonmembers was available only for the American Medical Association and the Southern Medical Association.

Table 9 presents information compiled by the author from brochures received from five national organizations. During 1976-1977 and 1978-1979, there has been a noticeable increase in the tuition for both members and nonmembers of each of these organizations.

Through the continuous collection of brochures from schools of medicine it has been possible to make a comparison between the 1976-1977 and 1978-1979 charges per hour of CME for ten medical schools. This material is tabulated in Table 10. All but two of the schools have increased the fees charged for their CME programs. The reasons for higher tuition fees are increased costs of

TABLE 6.—*Determination of Cost per Hour of CME in Eight Hospitals in Sacramento, California, 1977-1978*

	Percentage of CME Cost From					*Cost Paid per Hr by*	
Hospital	*Hospital*	*Physician*	*Pharmaceutical Grants*	*CME Hrs Offered/Yr*	*Cost /Hr*	*Hospital*	*Physician*
1	90	10	<1	200	$ 5.00	$ 4.50	$ .50
2	89.35	8.75	1.9	240	8.58	7.83	.75
3*.....	13.06	1.22+	0	30	20-30	2.61-3.92	.36
4†.....	86.7	13.3	0	149	5.15	4.47	.68
5	90	10	0	10	14.35	12.92	1.43
6	10	40	50	129	5.00	.50	2.00
7	75	25	0	125	12.00	9.00	3.00
8	100	0	0	500	4.93	4.93	0.00

CME = Continuing Medical Education

*This hospital indicated that 85.7 percent of CME cost was donated time by staff physicians.
†Estimated cost based on limited data.

TABLE 7.—*Support for CME Programs Sponsored by California Organizations and Societies, 1977-1978*

Organization or Society	*Cost/Hr*	*Membership Dues (Percent)*	*Course Fee (Percent)*	*Foundation Grants (Percent)*	*Pharmaceutical Grants (Percent)*	*Other Support*
1	$<5.00	100				
2	<5.00		50	Yes		
3	10.00-15.00	100				
4	No charge	100				
5	No charge	100				
6	No charge	100				
7	<5.00	95		5		
8	<5.00	20.2	51.5		7.7	20.5% (dinner)
9	No charge	100				
10	5.00-10.00	100				
11	No charge	100				
12	No charge	100				$10.00-15.00 (meals)
13	<5.00	100				$ 5.00- 7.00 (meals)
14	<5.00	100				
15	10.00-15.00	90		10		
16	10.00-15.00	90				10%
17	>15.00	30		30	30	10% (medical staff wives)
18	<5.00	70			10	20% (sale of exhibit space)

salaries, mailing lists, postage, printing, food and other expenses related to program development and presentation.

Discussion

The amount of money that a physician pays to attend a CME program is the sum of costs for tuition, travel, room and board, and incidental expenses, which must be added to his loss of income and continuing office expenses during his absence. The sum is modified by the length of the program, the distance from his home, his tax bracket and what portion of these expenses are tax deductible.

The cost of developing a CME program by a provider such as a medical school, a hospital or a medical society is the total amount of money expended for honoraria; travel and per diem of faculty; preparation of a syllabus; development of a brochure describing the program; purchase of mailing lists of persons to whom the brochure will be sent; postage; staff time required to develop and present the program; charges for meeting rooms, coffee breaks, food, and social func-

TABLE 8.—*Tuition Charged for CME Programs by National Organizations, 1976*

Organization	Tuition		Tuition per Hour	
	Member	Nonmember	Member	Nonmember
American Academy of Orthopedic Surgeons	$150	$200		
American Society of Plastic and Reconstructive Surgeons	250	300		
American Academy of Pediatrics	115	150		
American Association of Anesthesiologists	75	100		
American College of Obstetricians and Gynecologists	120	120		
American Medical Association			$10.00	$15.00
Southern Medical Association			10.00	10.00/+20.00

CME=Continuing Medical Education

TABLE 9.—*CME Program Charges by Five National Organizations and Societies*

Organization or Society	1976-1977			1978-1979		
	No. of Programs	Member and Nonmember Tuition/Hr (Range)	Average per Hr	No. of Programs	Member and Nonmember Tuition/Hr (Range)	Average per Hr
American Heart Association	39	M $1.67-16.07	$ 7.48	10	$ 1.25-16.60	$ 9.20
		NM 1.67-17.86	8.89			
American College of Cardiology	44	M 5.30-16.07	8.48	4	M 5.26-12.86	8.87
		NM 8.70-14.64	10.52		NM 6.57-15.71	11.05
American College of Physicians	27	M 4.65- 9.02	6.69	14	M 8.47-13.21	10.57
		NM 6.89-13.08	9.79		NM 11.29-17.65	14.09
American Medical Association	62	M 2.73-13.33	11.03	36	M 10.00-13.33	11.33
		MN 2.73-18.33	13.73		NM 10.83-18.33	16.77
American College of Chest Physicians	27	M 4.65- 9.02	6.69	6	M 7.22-11.54	8.64
		NM 6.89-13.08	9.79		NM 7.22-13.46	9.76

M=member
NM=nonmember

TABLE 10.—*Comparison of Medical School Tuitions for CME Between 1976-1977 and 1978-1979*

Medical College	1976-1977			1978-1979		
	No. of Programs	Range	Average	No. of Programs	Range	Average
1	52	$ 0-10.00	$ 6.97	8	$7.50-13.75	$ 9.97
6	123	5.63-13.16	9.00	22	5.84-11.11	8.81
7	65		8.32*	13	4.17-16.67	10.81
29	5	5.00- 8.33	6.56	10	5.76-12.50	7.38
41	38	0-18.75	5.35	73	0-16.67	9.21
49	32	6.36-10.00	10.00*	10	7.43-14.00	9.51
50	19	2.00-14.10	5.43	6	4.35-11.28	7.86
53	13	2.00-23.44	8.97	10	7.14-15.00	10.43
54	30	4.00-15.00	7.18	20	5.00-13.64	8.69
55	49	3.57-17.86	9.43	30	6.25-15.38	10.44

CME=Continuing Medical Education

*Estimate from questionnaire

tions, if included; preparation of name tags; handling of registration fees; rental of audiovisual equipment; telephone costs; back-up personnel; maintenance of a list of the attending physicians for accrediting agencies; evaluation of the course, and the necessary bookkeeping to reconcile income and expenditures. The tuition charged by the sponsor must represent an educated guess of the total cost of the program divided by the anticipated number of persons attending. The tuition charged can be reduced if a pharmaceutical company provides support or if the sponsoring school or organization supports the staff members or program activities of the department responsible for continuing education activities.

Because accredited CME is offered by many diverse providers, a physician has a wide choice of programs he can attend and expenses he can pay for continuing education. Expenditures will be minimal if a physician practices near a medical school that offers tuition-free Category I credit for grand rounds and other educational activities. Expenses will also be minimal if CME is obtained through the hospital in which a physician practices or through a local professional organization or society.

While the above sources of CME may provide an adequate number of accredited hours to allow physicians to satisfy the requirements of a state licensing agency or a professional organization that requires CME attendance for continued membership, the educational material presented may not be adequate or appropriate for a particular physician's perceived or actual needs.

CME programs given in a physician's own community have the disadvantage that, by virtue of obligations to patients, the physician is often required to leave the CME program during its presentation, or is unable to attend at all.

These deterrents to participation in CME presentations in his own community may require that a physician seek his continuing education away from his own community, at courses sponsored by medical schools, professional organizations and societies, or commercial purveyors of CME.

This study did not examine the costs and availablity of commercial sponsors of CME that have been organized to present programs to health professionals. These groups have proliferated during the last several years and offer attractive programs in the larger cities, in resort areas or aboard ships. The actual CME programs are presented by outstanding teachers recruited from medical schools, research institutions and private practice. Because most are nonprofit corporations, some of which have been organized by pharmaceutical companies, they represent serious competition to the schools of medicine—both in the use of the same faculty members and in presenting programs that attract and compete for the same audience that the medical schools are seeking.

Tuition charged by schools of medicine definitely varies in the four designated regions of the United States.

Medical schools in the Northeastern region had the highest course tuition (school 4—$1,300.00), the highest per hour tuition charge (school 10—$44.44), the highest average charge per hour (school 10—$11.19), and the highest average regional charge—$8.06.

Similar data for the West were as follows: highest course tuition (school 50—$425.00), highest per hour tuition charge (school 53—$23.44), highest average charge per hour (school 52—$10.47) and average regional charge of $7.09.

The Midwestern schools and those located in the South and Southwestern area reported tuition charges that were lower than the Northeast and the West and had average regional charges of $6.68 and $6.36, respectively.

The hourly charges reported by the 55 medical schools surveyed in this study are less than those reported by Lockard.[3] He indicated that of 37 medical schools, graduate schools and hospitals the average cost per CME hour was $10.04, with a range of $2.50 to $21.25. Similar data for 53 medical schools surveyed in this study that supplied calculable charges indicate that the average cost per CME hour is $7.33, with a range of 0 to $44.44. Because the number of medical schools (as compared to graduate schools and hospitals) is not indicated by Lockard, this difference could be explained if he had included a small number of medical schools or if the schools of medicine were located primarily in the Northeastern area of the United States.

No pattern or explanation could be found to explain the variations in tuition charged for CME programs by medical schools that received financial support, compared with those that did not. One factor examined was the size of the community or city in which the school was located. No identifiable pattern was apparent. The amount of medical school support did not appear to affect the tuition charged. Items that should

be examined to answer this question include location of the program, the number of visiting faculty, and inclusion in the tuition of the cost of meals, banquets and lodging, as well as the availability of these support dollars for investigation into needs assessment, evaluation and innovative techniques of adult education. The data requested in the survey questionnaire did not include this area of CME.

Of interest, but of little assistance in answering this question, was the observation that of 30 schools that had tuition charges that were higher than their regional average, 15 (50 percent) received some support for their CME activities from their parent organizations. Of the 20 schools that presented programs with tuition charges lower than the area average, 15 (75 percent) received support from the medical schools. Thus, of the 52 schools that responded to this question, 30 (58 percent) received support for their CME activities. This reflects unfavorably on those schools in California, where only two of eight received support for their CME activities. Both of these schools are privately supported. One school had an average tuition charge above the regional average ($9.80) and the other below ($6.12).

Oetting[1] in 1978 reported that the American Medical Association charged its members $10 per clock hour for CME. The present review of 62 CME programs offered by the AMA shows a range of tuition between $2.73 per clock hour and $13.13, with an average charge for members of $11.03. The average charge for nonmembers was $13.73.

Analysis of 36 programs sponsored by the AMA during 1978-1979 showed an average member charge per hour of $11.33 and nonmember charge of $16.77. The fees charged by the American Medical Association were appreciably higher than the other four national organizations whose CME brochures were reviewed.

The finding that a large number of hours of Category I CME credit is available from schools of medicine in California at no cost to physicians is noteworthy, and probably is true of other medical colleges throughout the United States. Unfortunately, this question was not included in our survey.

Clearly, the relatively low cost of continuing medical education per hour in the small sample of California hospitals needs verification. A survey of hospitals in California accredited for continuing medical education is now being conducted to supplement the data presented here and will be reported in a subsequent paper.

In California, the courses sponsored by statewide medical societies and organizations, including the Postgraduate Institutes cosponsored by the California Medical Association, also provide CME to physicians at a relatively low charge. Even though these courses may be held in cities or areas which are not near their practices, the total cost to physicians remains relatively low.

Conclusion

It appears that a physician may pay as little or as much as he or she wishes for accredited continuing medical education. CME programs are available in hospitals, at medical centers and through statewide professional organizations at little or no cost. Often these programs are presented during a lunch or dinner meeting in the physician's own hospital or community so that he may attend these with little or no loss of time from his professional activities. While the lecturers may be the physician's peers, the opportunities for learning and exchange of information are present. Further, many of these meetings feature a medical authority who is available to that institution at little or no cost.

For a physician who, for one reason or another, desires to attend continuing medical education programs in settings other than in his or her own community, such programs abound throughout the United States and the world. Obviously, the cost of the continuing education will be higher because of increased tuition, and the cost of travel, meals and other expenses. However, for the reasons given earlier, the opportunity to attend CME programs away from pressures of the office and practice may justify the additional expense.

The choice of where a physician obtains continuing medical education and how much is paid for it is a decision that must be made individually. It should be based on the physician's own needs and the methods of learning best suited to meet them, as well as how much he or she wishes to pay for upgrading professional and educational competence.

REFERENCES

1. Oetting GD: The cost of getting educated. AMA Cont Med Ed Newsl 7:8-10, Sep-Oct 1978

2. Lockhard WT Jr: Survey of costs of continuing medical education programs. AMA Cont Med Ed Newsl 7:2-4, Aug 1978

3. Miller LA: Sharp boost in CME costs cited. Am Med News 21:3, Dec 22-29, 1978

in memoriam

California Medical Association

ADAMS, CLARENCE W., San Francisco. Died October 10, 1979 in San Francisco, aged 93. Graduate of Rush Medical College, Chicago, 1916. Licensed in California in 1919. Dr. Adams was a member of the San Francisco Medical Society.

AWTREY, HUGH H., Fresno. Died November 25, 1979 in Fresno, aged 77. Graduate of Meharry Medical College, Nashville, 1929. Licensed in California in 1936. Dr. Awtrey was a retired member of the Fresno-Madera Medical Society.

BERCOVITZ, NATHANIEL N., Pasadena. Died October 13, 1979, aged 90. Graduate of the University of California Medical School, Berkeley-San Francisco, 1914. Licensed in California in 1914. Dr. Bercovitz was a member of the Los Angeles County Medical Association.

CASSEL, MELVIN A., Orange. Died in November 1979, aged 63. Graduate of St. Louis University School of Medicine, 1938. Licensed in California in 1971. Dr. Cassel was a member of the Orange County Medical Association.

EDWARDS, J. ALTON, Yucaipa. Died January 7, 1980 in Yucaipa of cerebrovascular accident, aged 62. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1941. Licensed in California in 1941. MD degree from California College of Medicine, 1962. Dr. Edwards was a member of the San Bernardino County Medical Society.

ENGEL, EDWARD E., Riverside. Died December 9, 1979 in Riverside, aged 78. Graduate of the University of Minnesota Medical School, Minneapolis, 1929. Licensed in California in 1929. Dr. Engel was a retired member of the Riverside County Medical Association.

FARR, WALTER H., Salinas. Died December 2, 1979 in Salinas, aged 78. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1928. Licensed in California in 1928. Dr. Farr was a retired member of the Monterey County Medical Society.

JELINEK, VACLAV V., Los Angeles. Died January 1, 1979, aged 66. Graduate of Beogradskog Universiteta, Medecinski Fakultet, Belgrade, 1938. Licensed in California in 1953. Dr. Jelinek was a member of the Los Angeles County Medical Association.

KELLY, HAROLD R., Sacramento. Died January 6, 1980 in Columbia of carcinoma of the pleura, aged 70. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1947. Licensed in California in 1949. Dr. Kelly was a retired member of the Sacramento County Medical Society.

KEMPF, PAUL R., JR., Encino. Died January 24, 1980 in Las Vegas of cancer, aged 55. Graduate of the University of Michigan Medical School, Ann Arbor, 1948. Licensed in California in 1953. Dr. Kempf was a member of the Los Angeles County Medical Association.

MALEK, KENNETH ROBERT, San Luis Obispo. Died January 25, 1980 of injuries received in automobile accident near Gaviota, aged 58. Graduate of the University of Southern California School of Medicine, Los Angeles, 1956. Licensed in California in 1957. Dr. Malek was a member of the San Luis Obispo County Medical Society.

MILLER, HAROLD, Los Angeles. Died January 5, 1980, aged 65. Graduate of the University of California Medical School, Berkeley-San Francisco, 1946. Licensed in California in 1946. Dr. Miller was a member of the Los Angeles County Medical Association.

OFFERMAN, ROBERT J., Santa Barbara. Died December 30, 1979 in Santa Barbara, aged 44. Graduate of State University of Iowa College of Medicine, Iowa City, 1961. Licensed in California in 1965. Dr. Offerman was a member of the Medical Society of Santa Barbara County.

RUTHERFORD, FINDLAY P., San Jose. Died January 28, 1980 in San Jose, aged 79. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1932. Licensed in California in 1932. Dr. Rutherford was a retired member of the Santa Clara County Medical Society.

STERN, MELVYN E., Anaheim. Died November 19, 1979, aged 44. Graduate of the University of Mississippi School of Medicine, 1961. Licensed in California in 1966. Dr. Stern was a member of the Orange County Medical Association.

UYEYAMA, KAHN, Pinole. Died December 30, 1979 in Pinole, aged 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1934. Licensed in California in 1934. Dr. Uyeyama was a retired member of the San Francisco Medical Society.

Utah State Medical Association

BRADSHAW, FREDERIC WILLIAM, Salt Lake City. Died December 21, 1979 in Salt Lake City, aged 64. Graduate of the University of Oregon Medical School, Portland, 1941. Licensed in Utah in 1971. Dr. Bradshaw was a member of the Salt Lake County Medical Society.

SPENCER, MAX JAY, Provo. Died November 22, 1979 in Provo, aged 54. Graduate of the University of Maryland School of Medicine, Baltimore, 1957. Licensed in Utah in 1965. Dr. Spencer was a member of the Utah County Medical Society.

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DAVID MULKEY, MD, Moderator

8:15 OVERVIEW OF COMMUNITY HEALTH PROBLEMS
OTTO H. RAVENHOLT, MD, Director, Clark County District Health Department

9:00 PRENATAL ABUSE AND SELF-NEGLECT
WILLIAM G. WIXTED, MD, Professor of Gynecology, University of Nevada School of Medicine

9:45 Coffee break

10:00 RESPIRATORY DISTRESS SYNDROME: RECOGNITION, TREATMENT AND PREVENTION
BERNARD H. FELDMAN, MD, Director, Southwest Neonatal Intensive Care Unit, Sunrise Hospital

10:45 DRUGS FOR STREET WEAR
STEVEN B. KARCH, MD, Co-Director, Emergency Department, Southern Nevada Memorial Hospital

11:30 SESSION WRAP-UP

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Afternoon Session

1:30 DEATH AND DESTRUCTION IN THE DESERT
G. SHELDON GREEN, MD, Clark County Medical Examiner

2:15 COUGHS AND WHEEZES—A SMOKE SCREEN
PAUL A. STEWART, MD, Respiratory Associate, Southern Nevada Memorial Hospital

3:00 Coffee break

3:15 BURNS, BUMPS AND AGING: SHEDDING LIGHT ON SUNSHINE
R. KENNETH LANDOW, MD, Assistant Clinical Professor of Medicine, University of Southern California School of Medicine

4:00 CLOSING REMARKS
DAVID MULKEY, MD

4:30 Adjournment

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANALYTICAL PROCEDURES FOR THERAPEUTIC DRUG MONITORING AND EMERGENCY TOXICOLOGY—Randall C. Baselt, PhD, Associate Professor, Department of Pathology; Director, Toxicology and Drug Analysis Laboratory, University of California Medical Center, Sacramento. Biomedical Publications, P.O. Box 495, Davis, CA (95616), 1980. 316 pages, $35.00.

A COMPREHENSIVE GUIDE FOR CANCER PATIENTS AND THEIR FAMILIES—Ernest H. Rosenbaum, MD, Associate Chief of Medicine, Mount Zion Hospital and Medical Center, Associate Clinical Professor of Medicine, University of California, San Francisco, Medical Director of San Francisco Regional Cancer Foundation and Special Care Unit at Marshal Hale Memorial Hospital, San Francisco; and Isadora R. Rosenbaum, Medical Assistant, San Francisco. Bull Publishing Co., P.O. Box 208, Palo Alto, CA (94302), 1980. 300 pages, $19.95 (clothbound); $11.95 (paperback).

COUNSELING IN GENETICS—Editors: Y. Edward Hsia, Departments of Genetics and Pediatrics, John A. Burns School of Medicine, University of Hawaii at Manoa; Kurt Hirschhorn, Division of Medical Genetics, Department of Pediatrics, Mt. Sinai School of Medicine, New York City; Ruth L. Silverberg, Department of Pediatrics, Yale University School of Medicine and Genetics Clinic, Yale University, New Haven, CT; and Lynn Godmilow, Division of Medical Genetics, Department of Pediatrics, Mt. Sinai School of Medicine, New York City. Alan R. Liss, Inc., 150 Fifth Ave., New York City (10011), 1979. 347 pages, $34.00.

CURRENT MEDICAL DIAGNOSIS & TREATMENT 1980—Marcus A. Krupp, MD, Clinical Professor of Medicine Emeritus, Stanford University School of Medicine, Director of Research, Palo Alto Medical Research Foundation, Director of Laboratories, Palo Alto Medical Clinic; Milton J. Chatton, MD, Clinical Professor of Medicine, Stanford University School of Medicine, Senior Attending Physician, Santa Clara Valley Medical Center, San Jose, Research Associate, Palo Alto Medical Research Foundation; and associate authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1980. 1,116 pages, $19.00.

DECISION FOR LIFE—Portraits of Living—Ernest H. Rosenbaum, MD, Associate Chief of Medicine, Mount Zion Hospital and Medical Center, Medical Director, San Francisco Regional Cancer Foundation, Associate Clinical Professor of Medicine, University of California, San Francisco, Medical Director, Special Care Unit, Marshal Hale Memorial Hospital, San Francisco; with Tina Anderson, William Cohen, MD, and Isadora Rosenbaum. Bull Publishing Co., P.O. Box 208, Palo Alto, CA (94302), 1980. 90 pages, $5.95 (paperback).

DIAGNOSTIC APPROACHES TO THE MALFORMED FETUS, ABORTUS, STILLBORN, AND DECEASED NEWBORN—Part A of ANNUAL REVIEW OF BIRTH DEFECTS, 1978—Editors: Mitchell S. Golbus, MD, Associate Professor of Obstetrics/Gynecology and Pediatrics, Director of Prenatal Detection Center, University of California, San Francisco; and Bryan D. Hall, MD, Professor of Pediatrics, University of California, San Francisco; Associate Editor: Natalie W. Paul, The National Foundation; Assistant Editor: Florence Dickman, The National Foundation-March of Dimes. Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1979. 189 pages, $22.00.

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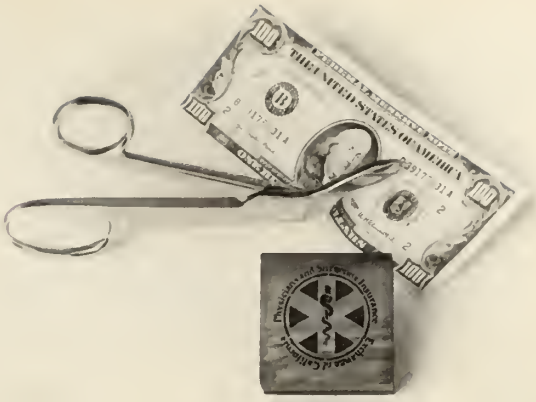

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(Continued from Page 20)

PHYSICIANS WANTED

GENERAL INTERNIST. Critical care experience. Join cardiologist. Some knowledge of Spanish. Work Los Angeles area. Full partnership after one year. Send curriculum vitae. Box 6107, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

EXCELLENT OPPORTUNITY for Board-eligible or -certified Family Practitioners to join multi-specialty prepaid group practice in growing urban area. Excellent fringe benefits. Close to hospital facilities. Short drive to beaches, mountains, San Francisco Bay Area. Equal Opportunity/Affirmative Action Employer. Contact: Teri Alyami, MD, The Permanente Medical Group, 5755 Cottle Road, San Jose, CA 95123 or phone (408) 578-0300.

OCCUPATIONAL MEDICINE RESIDENCY—The University of Utah has a challenging occupational and environmental medicine residency/fellowship program funded by a NIOSH Educational Resource Center. Two-year program leads to Master of Science in Community Medicine (MPH equivalent), a research thesis, clinical training and preceptorships with industry and labor. Combined programs with family practice (4 years) and in pulmonary disease for internists (3 years) are available. First year clinical training can be provided. Contact: John C. Elliott, MD, MSc, Director, OM Residency, RMCOEH, Bldg. 112, University of Utah, Salt Lake City, Utah 84112. The University of Utah is an Equal Opportunity Employer.

PEDIATRIC CARDIOLOGIST—Experienced in two dimensional echocardiography needed to complement group of active cardiologists in suburb of Los Angeles. Excellent fringe benefits—salary commensurate with experience. Please send CV to Box 6108, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNAL MEDICINE/CARDIOLOGY. Board certified or board eligible internists/cardiologists needed for the Marysville-Yuba City area, located in the middle of the Sacramento Valley, forty miles to the north of Sacramento, California. Medical service area consists of approximately 125,000 and presently has a noticeable shortage of internists/cardiologists. New and remodelled medical facility in Marysville consisting of 128 bed acute hospital, 24-hour physician staffed emergency facility, modern up-to-date ICU/CCU and soon-to-establish CT scanner and neurosurgical service. Marysville and Yuba City are just a couple of hours from Reno, Lake Tahoe, San Francisco and the Pacific Ocean. Excellent opportunity for the arts and unlimited outdoor life including skiing, camping, gold panning, boating, water sports, hunting and fishing in surrounding lakes and rivers. Hospital willing to aid in relocation and establishment of medical office practice. Excellent opportunity. Please contact Greg Posner, Assistant Administrator, Rideout Memorial Hospital, 726 Fourth Street, Marysville, CA 95901 or call collect (916) 742-7381, Ext. 551.

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PHYSICIANS WANTED

OB-GYN, COMPLETING RESIDENCY, Bd elig/qual, to join well-established multispecialty group including 3 OB-GYN specialists. Located in the most beautiful part of the San Fernando Valley. Excellent salary depending on experience. Superb, noncontributory retirement, paid malpractice, etc. Partnership available, many other benefits. Write and send CV to Mr. Norman Veis, Administrator, 10660 White Oak, Granada Hills, CA 91344.

MEDICAL ONCOLOGIST needed to join Hematology-Oncology practice in Southern California, one hour from Los Angeles. Available immediately. Reply to Box 6109, Western Journal of Medicine, 731 Market St. San Francisco, CA 94103.

ORTHOPEDIC SURGEON—Board Certified, Orthopedic Surgeon needed at VA Medical Center, Livermore, CA. Ideal living, good climate and clean air. Malpractice insurance not needed. Position available at present. Salary dependent upon experience and qualifications. Contact: John F. Kane, MD, Chief of Staff, VA Medical Center, Livermore, CA 94550. Tel: (415) 447-2560, ext 204.

FAMILY PRACTICE. Board certified or board eligible family practitioners needed for the Marysville-Yuba City area, located in the middle of the Sacramento Valley, forty miles to the north of Sacramento, California. Medical service area consists of approximately 125,000 and presently has a noticeable shortage of family practitioners. New and remodelled medical facility in Marysville consisting of 128 bed acute hospital, 24-hour physician staffed emergency facility, modern up-to-date ICU/CCU and soon-to-establish CT scanner and neurosurgical service. Marysville and Yuba City are just a couple of hours from Reno, Lake Tahoe, San Francisco and the Pacific Ocean. Excellent opportunity for the arts and unlimited outdoor life including, skiing, camping, gold panning, boating, water sports, hunting and fishing in surrounding lakes and rivers. Hospital willing to aid in relocation and establishment of medical office practice. Excellent opportunity. Please contact Greg Posner, Assistant Administrator, Rideout Memorial Hospital, 726 Fourth Street, Marysville, CA 95901 or call collect (916) 742-7381, Ext. 551.

SITUATIONS WANTED

FAMILY DOCTOR: Practice sought in central or eastern San Diego County. Partnership size or potential. Terms desired for immediate or future takeover. (714) 464-6911 evenings, or Box 6105, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CARDIOLOGY INTERNIST, 31, ABIM, University trained in Invasive and Noninvasive Cardiology seeks private practice, available July, 1980. Write Box 6101, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIAN with 10 years experience in preventive and occupational medicine and postgraduate training for 4 years, seeks position in San Francisco/Bay Area in medical outpatient clinic. Write Box 6020, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SITUATIONS WANTED

EMERGENCY DEPARTMENT, CRITICAL CARE PHYSICIAN—Airmobile available for part time coverage. ER and/or ICU-CCU. Well trained and experienced. Box 6099, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGIST, board certified, seeking locum tenens or full time general radiology position in Northern Calif. or Northwest States. Curriculum Vitae and references upon request. Fred W. King, MD, 497 Hartnell Place, Sacramento, Calif. 95825, (916) 929-5278.

PATHOLOGIST, 45, certified AP-CP, excellent references, seeks relocation to San Francisco-San Jose area for permanent full-time or part-time practice. Box 6110, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL PRACTITIONER—Experienced 30 yrs. Seeks opportunity for association, or to lease, or purchase modern office with gen. practice. Will consider any area in Calif. Write Box 6112, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIAN'S ASSISTANT—available summer 1980. Full national and California state certification; six years clinical experience including general practice, industrial medicine, geriatrics, psychiatry. Oriented to quality care and direct patient contact. Seeks active position with responsibility. Write, Box 6100, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

MEDICAL PRACTICES AVAILABLE

WELL ESTABLISHED PRACTICE of Internal Medicine, predominantly consultation. Associated with well equipped community hospital, in fast growing rural area 2½ hours north of San Francisco. Equipment, goodwill. Will stay to introduce. Minimum annual gross $120,000. Ideal place to live and practice. Write Box 6089, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

BUYING or **SELLING** any type Medical Practice contact California Professional Practices, 2555 Huntington Drive, Suite D, San Marino, CA 91108. (213) 796-9262, Eve (213) 355-3983 and 21 Altamount Dr., Orinda, CA 94563. (415) 376-0762.

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INFORMATION

(415) 777-2000

EX 220

MEDICAL PRACTICES AVAILABLE

MONTEREY PENINSULA, CA—100 miles south of San Francisco. Well established Family Practice. Available 1 April. 2,200 sq. ft. Suitable for one or two Doctors. X-ray, ER and large business office. Average 200 patients per week with excellent collections. Medical building to be leased. Reply Box 6103, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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PRACTICES FOR SALE

ESTABLISHED OPHTHALMOLOGY PRACTICE. Santa Cruz County, California. Completely equipped office. Reason available: 1 ophthalmologist in Navy, other wishes semi-retirement. Willing to stay on cover/assist. Andrew S. Markovits, MD, 6809 Kitty Hawk, Pensacola, FL 32506. (904) 456-0903.

PRIMARY SOLO MEDICINE, SALINAS. Reasonable rent, all supportive medical services, hospital nearby. Medical and office equipment, furniture, files. $9,000. Practice free for patient care. Any financing agreeabe. call (408) 422-5798 after 5 p.m.

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OFFICES FOR LEASE OR RENT

CALIFORNIA BAY AREA OPPORTUNITY for pediatrician or family physician. Fully equipped pediatric/adult office immediately available in 22,000 population San Lorenzo, close to open staff hospitals, Oakland and San Francisco. Phone or write: Ivar Tegnar at 3636 Castro Valley Blvd., Castro Valley 94546, tel: (415) 581-4914 for details including very low rental during initial period of lease.

SOQUEL CALIFORNIA. 1,200 sq. ft. medical office. 3 extra-large exam rooms, surgery. Extras include handicap facilities, ample parking, on bus line. Furniture, office equip. negotiable. Andrew S. Markovits, MD, 6809 Kitty Hawk, Pensacola, FL 32506. (904) 456-0903.

BEAUTIFUL SOUTHERN CALIFORNIA HIGH DESERT—Office space available in new medical office building on grounds of new 56-bed rural community hospital 125 miles from Los Angeles. Contact Marvin J. Friedenberg, MD, Hi-Desert Medical Center, P.O. Box 1226, Joshua Tree, CA 92252.

MEDICAL BUILDING

BUILDING FOR LEASE. All/part. Eight offices, laboratory, radiology laboratory, pharmacy, walk-in vault. Convenient to hospital. Fifty miles NW of San Francisco. For information write: P.O. Box 262, Napa, CA 94558. Available May 1, 1980.

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CHULA VISTA, CA—1,100 sq. ft. medical office in medical professional center. One block from large community hospital, on major thoroughfare. Available immediately for rent or lease. Has x-ray capability and minor surgery. For information contact physician owners (714) 427-1536 or (714) 422-9283 or write Bahia Professional Center, 353 H St., c/o Suite F, Chula Vista, CA 92010.

PALOS VERDES PENINSULA Palos Verdes Medical Center Medical Suite For Lease. Excellent support services—Pharmacy—Pathology Lab Radiologist—Ample Parking—Redecorate to Suit. Call (213) 377-6450.

TO LEASE: Aptos, Calif. 1,600 Sq. Ft. in newly constructed professional building. Ideal location for physician in coastal California. Remaining space occupied by a pedodontist and an orthodontist. Call Jim Jacobson, DDS, 1-408-722-5022.

MEDICAL SUITE FOR LEASE OR PURCHASE San Clemente (Calif.)—2 year old office, 1,200 sq. ft. with 3 exam rooms, x-ray/lab in downtown coastal city. Ideal area to develop practice. Parking, beautiful office, good terms, lease or sell. Robert E. Dyer, 23561 Paseo de Valencia, Laguna Hills, CA 92653. Phone (714) 951-8561.

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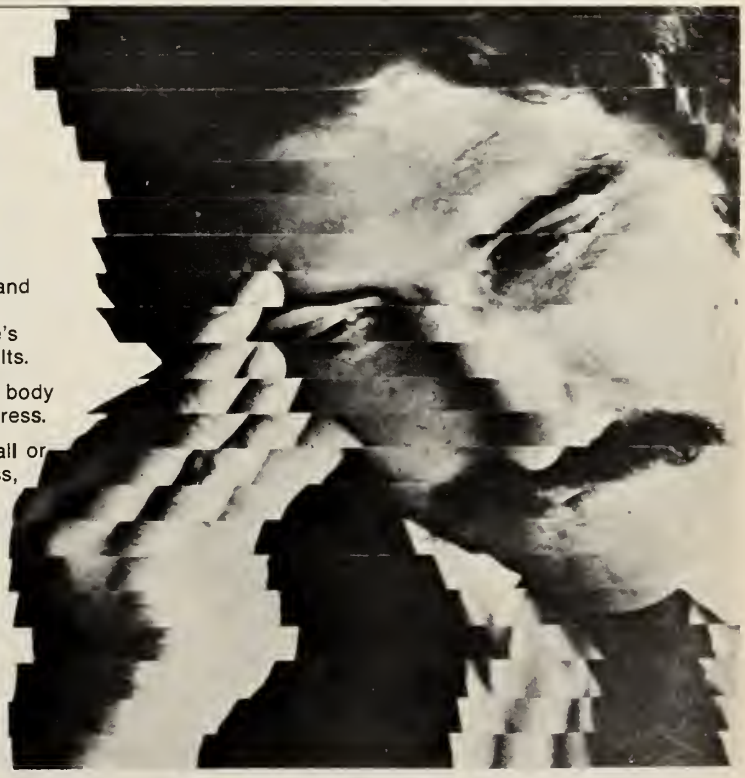

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This listing of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

September 13-20—**Anesthesiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

CANCER

May 26-27—**American Society of Clinical Oncology.** Town and Country Hotel, San Diego. Monday-Tuesday. Contact: A. Van Horn, III, Exec. Dir., 435 N. Michigan Ave., Chicago 60611.

EMERGENCY MEDICINE

April 17—**Infectious Disease for Emergency Physicians.** Goleta Valley Community Hospital and Assn. for Emergency Physicians for Ventura and Santa Barbara Counties at Goleta Valley Hosp., Santa Barbara. Thursday. 1½ hrs. CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

April 17—**Neurologic Emergencies.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

April 21-25—**Postgraduate Institute for Emergency Physicians,** Symposium I. UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

April 25-27—**Advanced Cardiac Life Support Provider, Recertification and Instructor Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, Education Dept., 2310 Mason St., San Francisco 94133. (415) 956-5900.

May 5-11—**Emergency Surgical Problems.** White Memorial Medical Center and LLU at Honolulu and Maui, Hawaii. One week. 24 hrs. $250. Contact: Dir., Cont. Med. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000, ext. 1460.

May 8-9—**2nd Annual Trauma Seminar.** DREW at Disneyland Hotel, Anaheim. Thursday-Friday. 14 hrs. Contact: Diane Anderson, Dept. of Surgery, Div. of Emergency Medicine, Charles R. Drew Postgraduate Med. Sch., 1621 E. 120th St., Los Angeles 90059. (213) 603-5235.

May 10-11—**Advanced Cardiac Life Support Provider Course.** DREW at Disneyland Hotel, Anaheim. Saturday-Sunday. 12 hrs. Contact: Diane Anderson, Dept. of Surgery, Div. of Emergency Medicine, Charles R. Drew Postgraduate Med. Sch., 1621 E. 120th St. Los Angeles 90059. (213) 603-5235.

May 11-17—**Modern Trends in Emergency Medicine.** Univ. of Hawaii, John A. Burns School of Medicine, Hawaii. One week. Contact: Delia M. Chang, CME, Univ. of Hawaii, John A. Burns Sch. of Medicine, 1960 East-West Rd., Honolulu 96822.

May 14—**Emergency Medicine Symposium.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Mem. Hosp., 5th Ave. and Esplanade, Chico 95926. (800) 822-8102, ext. 284.

May 15—**ENT Emergencies.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

May 19-23—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 40 hrs. $300.

May 27-31—**American College of Emergency Physicians, California Chapter—1980 Scientific Assembly.** ACEP, Calif. Chap., and UCSD at Hotel del Coronado, Coronado. Tuesday-Saturday. Contact: UCSD.

June 4-8—**Seminar in the Sierra: Advanced Course in Emergency Medicine.** Doctor's Essential Services, Inc.; Providence

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

Hospital, Oakland; and Emergency Physicians, San Leandro, at Stanford Sierra Lodge, Fallen Leaf Lake, Lake Tahoe. Wednesday-Sunday. 21 hrs. $260. Contact: Maureen E. Dvorak, DES, 897 MacArthur Blvd., San Leandro 94577. (415) 632-1504.

June 10-13—**Radiology in the Emergency Room Department.** UCSF at Fairmont Hotel. Tuesday-Friday.

June 17—**Death in the Emergency Department.** St. John's Hospital and Assn. for Emergency Physicians for Ventura and Santa Barbara Counties at St. John's Hospital, Oxnard. Tuesday; 8:00 p.m. 1½ hrs CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

June 19—**Plastic Surgery in the Emergency Department.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

June 20-22—**Recognition and Management of Poisonings and Toxicological Emergencies.** UCSF, S.F. Bay Area Reg. Poison Control Ctr., Am. Assn. of Poison Control Ctrs. and Am. Academy of Clinical Toxicology at Jack Tar Hotel, San Francisco. Friday-Sunday. 17 hrs. Contact: Dr. Kenneth W. Lem, UCSF, San Francisco 94143. (415) 666-4194.

June 23-27—**Advanced Emergency Medicine.** STAN. Monday-Friday. 25 hrs. $290.

June 23-27—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

June 27-28—**Ophthalmology and ENT for Emergency Room Physicians.** PMC. Friday-Saturday. 12 hrs.

July 14-18—**Medical Management of EMS Systems.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs.

July 21-25—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

July 25-27—**Advanced Cardiac Life Support Provider, Recertification and Instructor Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, Education Dept., 2310 Mason St., San Francisco 94133. (415) 956-5900.

August 11-15—**Postgraduate Institute for Emergency Physicians, Symposium I:** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

September 18—**Abdominal Trauma.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

MEDICINE

April 16—**Percutaneous Angioplasty.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 4 hrs. $35. Contact: Janie Sternal, Coordinator, Cont. Med. Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8904 or (213) 488-8123.

April 18-20—**Rheumatology: The New Decade.** UCSF, The Cypress Foundation and Monterey Co. Medical Society at Del Monte Hyatt House, Monterey. Friday-Sunday. 16 hrs. $155. Contact: UCSF.

April 25-27—**New Concepts in Clinical Electrocardiography.** American College of Cardiology at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 28-30—**Pediatric Dermatology.** STAN at Rancho Mirage. Monday-Wednesday. 18 hrs. $195.

April 30—**Office Management of Hypertension.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Wednesday. 4 hrs.

May 2-3—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Saturday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

May 2-4—**Headache Management: Therapeutic Workshops.** UCLA at Newporter Inn, Newport Beach. Friday-Sunday.

May 3—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

May 3—**Controversies in Internal Medicine.** San Jose Health Center at Marriott's Great America, Santa Clara. Saturday. 5 hrs. $50. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., San Jose Health Ctr., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

May 3-4—**Practical Rheumatology for the Primary Care Physician.** UCLA. Saturday-Sunday. 12 hrs. $160.

May 9-10—**Coronary Artery Disease 1980.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. 12 hrs. $120. Contact: Prog. Coordinator, MHMC-UCI Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

May 9-11—**The Many Faces of Headache.** UCD at Holiday Inn, Napa Valley. Friday-Sunday.

May 10—**Cardiology Conference.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

May 15-17—**Acute Myocardial Infarction.** PMC at St. Francis Hotel, San Francisco. Thursday-Saturday. 15 hrs.

May 16-18—**Cardiac Rehabilitation.** International Medical Education Corp. at Jack Tar Hotel, San Francisco. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

May 19-24—**4th Bi-Annual Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday.

May 30—**Team Approach to Arthritis.** PMC and Arthritis Foundation. Friday. 6 hrs. $85.

May 30-31—**Prevention and Treatment of Venous Thromboembolism.** Cedars-Sinai Medical Center, Los Angeles. Friday-Saturday. 9 hrs. $150. Contact: Lore Kahane, Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Rm 2049, Los Angeles 90048. (213) 855-5547.

May 31-June 1—**Pediatric Dermatology.** UCLA. Saturday-Sunday.

May 31-June 1—**Kidney Disease—20th Annual Scientific Symposium.** Kidney Foundation of Southern Calif. at Bonaventure Hotel, Los Angeles. Saturday-Sunday. Contact: Micki Faris, Kidney Fndn. of So. Calif., 6820 La Tijera Blvd., Suite 111, Los Angeles 90045. (213) 641-8152.

June 2-6—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday. 34 hrs.

June 3-October 14—**Internal Medicine Review.** UCLA. Tuesday evenings.

June 7—**Current Concepts in Cardiac Rehabilitation.** Am. Heart Assn., Greater L.A. Affiliate, at Biltmore Hotel, Los Angeles. Saturday. 6 hrs. $60, AHA member; $70, nonmember. Contact: Jan Stein, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

June 9-13—**Advances in Internal Medicine.** UCSF. Monday-Friday. 34 hrs.

June 11-14—**7th Annual Symposium on Clinical Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Sheraton

Harbor Island Hotel, San Diego. Wednesday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 18—**The Diagnosis and Management of the Newborn With Cardiorespiratory Disease.** American Heart Assn., Greater Los Angeles Affiliate, at New Otani Hotel, Los Angeles. Wednesday. 6 hrs. $50, member; $60, nonmember. Contact: Mary Frances Flynn, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

June 20-21—**Medical Knowledge Self Assessment—Group C.** American College of Physicians and PMC at Hyatt Regency, San Francisco. Friday-Saturday. Contact: PMC.

June 21-22—**American Association for the Study of Headache.** Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: S. Diamond, MD, Exec. Sec., 5252 N. Western Ave., Chicago 60625.

June 27-29—**Hepatobiliary Disease in Clinical Practice.** American College of Physicians at Holiday Inn on Union Square, San Francisco. Friday-Sunday. 15 hrs. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

July 8-10—**Podiatric Dermatology.** STAN. Tuesday-Thursday. 17 hrs.

July 11-13—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Hyatt Regency, San Francisco. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

July 12-19—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 23 hrs. $290.

August 2—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

August 8-9—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Saturday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

August 15-17—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

September 18-19—**Hypertension.** UCD at Sahara, Lake Tahoe. Thursday-Friday. 15 hrs.

September 25-26—**Annual Physicians' Symposium.** American Heart Assn., San Francisco Chapter, at San Franciscan Hotel, San Francisco. Thursday-Friday. Contact: Kari Olila, AHA, 421 Powell St., San Francisco 94102. (415) 433-2273.

September 26-27—**American Society of Internal Medicine.** Islandia Hyatt, San Diego. Friday-Saturday. Contact: ASIM, 2550 M St. NW, Suite 620, Washington, DC 20037.

September 26-28—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Hyatt on Union Square, San Francisco. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

OBSTETRICS AND GYNECOLOGY

May 12-14—**Recent Advances in Ob/Gyn.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

May 16-18—**Ob/Gyn.** UCLA at Ojai Valley Inn, Ojai. Friday-Sunday. 12 hrs. $300.

June 5-7—**Gynecologic Urology: Theory and Practice, Basic and Advanced.** Mem. Hosp. Med. Ctr.-UCI Ctr. for Health Education at Inn at the Park, Anaheim. Thursday-Saturday. 20 hrs. $300. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 10-16—**Obstetrics/Gynecology.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

September 5-6—**Environmental Hazards in Pregnancy: A Clear and Present Danger.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 12 hrs.

PEDIATRICS

April 26-27—**The Special Child.** See Psychiatry, April 26-27.

April 28-30—**Pediatric Dermatology.** See Medicine, April 28-30.

May 3—**Pediatric Dermatology Seminar.** See Medicine, May 3.

May 5-9—**Pediatric Review—10th Annual.** USC. Monday-Friday.

May 8-10—**Annual Pediatrics Course.** UCSF. Thursday-Saturday.

May 14-16—**Care of the Sick Newborn.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 19 hrs. $150. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 21-25—**Pediatrics for the Primary Care Physician.** UCD at Red Lion Motor Inn, Sacramento. Wednesday-Sunday. 18 hrs.

May 24-26—**Northern California Chapter, American Academy of Pediatrics—Annual Spring Meeting.** Del Monte Hyatt House, Monterey. Saturday-Monday. 8 hrs. $100, members; $125, nonmembers. Contact: Beverly Busher, NCCAAP, 422 Alexander Ave., Larkspur 94939. (415) 924-9613.

May 31-June 1—**Pediatric Dermatology.** See Medicine, May 31-June 1.

June 6-8—**Connective Tissue Disease.** American Academy of Pediatrics and Children's Hospital of Los Angeles at Bonaventure Hotel, Los Angeles. Friday-Sunday. Contact: Judy C. Hambourger, Cont. Ed., AAP, P.O. Box 1034, Evanston, IL 60204.

June 14-21—**Pediatric Workshop.** USC at Royal Lahaina, Maui, Hawaii. One week. 22 hrs. $325.

June 18—**The Diagnosis and Management of the Newborn With Cardiorespiratory Disease.** See Medicine, June 18.

August 2—**Pediatric Dermatology.** See Medicine, August 2.

September 18-20—**Pediatric Urology.** UCD at Holiday Inn, Napa Valley. Thursday-Saturday. 12 hrs.

PSYCHIATRY

April 18-20—**Northern California Psychiatric Society—Annual Spring Meeting.** Ahwahnee Hotel, Yosemite. Friday-Sunday. 6 hrs. Contact: NCPS, 1631 Ocean Ave., San Francisco 94112.

April 26-27—**The Special Child.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

May 4—**Psychiatric Aspects of Medical Practice and the Psychosocial Factors of Healing.** UCSF. Sunday. Contact: David H. Rosen, MD, Langley Porter Institute-Box 34B, 401 Parnassus Ave., San Francisco 94143. (415) 665-8282.

May 5-9—**American Psychiatric Association.** Hilton, San Francisco. Monday-Friday. Contact: APA, 1700 18th St. NW, Washington, DC 20009.

June 4—**Movement Disorders—Update 1980.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 6 hrs. $65. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

June 21-22—**Intellect and Illness.** UCLA. Saturday-Sunday.

June 22-27—**Comparative Psychotherapies.** USC at Hilton, San Diego. Monday-Friday.

RADIOLOGY AND PATHOLOGY

May 10—**Chest Radiology: Update 1980.** Northern Calif. Radiological Society at Red Lion Inn, Sacramento. Saturday. 7¼ hrs. $75. Contact: Richard C. Gross, MD, Roseville Community Hosp., Roseville 95678. (916) 783-9111, ext. 543.

May 17—**Recent Advances in Pathology.** UCSF at Hyatt on Union Square, San Francisco. Saturday. 8 hrs. $90.

May 28-30—**Present Concepts in Diagnostic Radiology.** Letterman Army Medical Center, San Francisco. Wednesday-Friday. 18 hrs. Contact: R. S. Pakusch, MD, or D. Kumar, MD, Dept. of Radiology, Letterman Army Med. Ctr., San Francisco 94129. (415) 561-3761.

June 6-8—**Spring Diagnostic Ultrasound Conference—5th Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 17 hrs. $250. Contact: Nathan Green, MD, 15107 Vanowen St., Van Nuys 91405.

June 10-13—**Radiology in the Emergency Room Department.** See Emergency Medicine, June 10-13.

June 16-25—**Radiology of Bone and Joint Disease.** UCSD at Hotel del Coronado, Coronado (June 16-19) and Kauai Surf Resort Hotel, Kauai, Hawaii (June 23-25). 7 days. 29 hrs. $500 (or $300 for first part; $200, second part).

June 22-27—**Pathology of the Lung.** UCSD. One week. 50 hrs. $450.

August 9-16—**Radiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

September 27-October 4—**Diagnostic Radiology.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

April 18-19—**Workshop on Orthopedic Injuries.** PMC. Friday-Saturday.

April 19-20—**Office Orthopedics/Office Urology.** UCLA. Saturday-Sunday.

April 24-25—**11th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. Contact: Mrs. Lu Hendricks, JSEI, UCLA Sch. of Med., Los Angeles 90024.

April 24-26—**General Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday.

April 26-May 3—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

April 28-30—**American Association for Thoracic Surgery.** Hilton Hotel, San Francisco. Monday-Wednesday. Contact: AATS, 6 Beacon St., Suite 620, Boston, MA 02108.

May 4-5—**Controversies in Surgery of the Colon, Rectum and Anus—5th Annual Clarence E. Stafford Memorial Surgical Symposium.** White Memorial Medical Center and LLU at Century Plaza Hotel, Los Angeles. Sunday-Monday. 11 hrs. Contact: Dir., Cont. Med. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000.

May 5-6—**Neurosurgical Contributions to Daily Medical Practice.** UCSD at Vacation Village, San Diego. Monday-Tuesday. 16 hrs. $160.

May 5-11—**Emergency Surgical Problems.** See Emergency Medicine, May 5-11.

May 9-10—**Combined Otolaryngologic/Orthognathic Symposium.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Friday-Saturday. 12 hrs. $195.

May 10—**Photocoagulation Therapy Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

May 15-17—**Nasal Plastic and Reconstructive Surgery.** PMC at Clift Hotel, San Francisco. Thursday-Saturday. 15 hrs. $250.

May 18-22—**American Urological Association.** Hilton, San Francisco. Sunday-Thursday. Contact: AUA, 1120 N. Charles St., Baltimore, MD 21201.

May 29-31—**Oto '80.** Project HEAR at St. Francis Hotel, San Francisco. Thursday-Saturday. 24 hrs. $485. Contact: Judy Staton Thielke, Project HEAR, 1801 Page Mill Rd., Palo Alto 94304. (415) 494-2000.

May 30-31—**Prevention and Treatment of Venous Thromboembolism.** See Medicine, May 30-31.

June 3-6—**1st Annual Verne T. Inman Lectureship and 15th Annual Scientific Program of the LeRoy C. Abbott Orthopaedic Society.** UCSF. Tuesday-Friday. 14 hrs. Contact: Judy Baca, Alumni Sec., UCSF, Room U471, San Francisco 94143. (415) 666-1166.

June 5-6—**Neurosurgery Postgraduate Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Friday. 17 hrs. $225.

June 6-7—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

June 7—**Glaucoma Surgery Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

June 7-13—**Orthopedic Review Course.** UCSF at Hyatt on Union Square, San Franciso. One week. 50 hrs.

June 8-14—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

June 11—**Problems in Postoperative Management and the Surgical Intensive Care Unit.** LLU. Wednesday. 4 hrs. $30.

June 14-21—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $325.

June 19-20—**Office Orthopedics.** USC. Thursday-Friday.

June 19-21—**Highlights of Ophthalmology.** PMC at Hyatt Regency, San Francisco. Thursday-Saturday. $225.

July 12-19—**Cardiovascular Medicine and Surgery: An Advanced Course.** See Medicine, July 12-19.

September 2-5—**IV International Symposium on Facial Nerve Surgery.** Ear Research Institute, Los Angeles. Tuesday-Friday. Contact: Facial Nerve Symposium, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

September 18-20—**Pediatric Urology.** See Pediatrics, September 18-20.

September 19-20—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

September 28-October 2—**American Academy of Otolaryngology.** Convention Center, Anaheim. Sunday-Thursday. Contact: AAO, 15 Second St. SW, Rochester, MN 55901.

OF INTEREST TO ALL PHYSICIANS

April 17-19—**Wound Management Workshop.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

April 21-25—**1980 Family Practice Review.** PMC at Hilton Hotel, Oakland Airport. Monday-Friday. 27 hrs. $350.

April 24-27—**Postgraduate Institute.** CMA and USC at Ahwahnee Hotel, Yosemite. Thursday-Sunday. Contact: Charlotte Newhart, CMA.

May 1-2—**Therapeutic Drug Monitoring.** PMC. Thursday-Friday. 12 hrs.

May 1-4—**4th Annual Basic Clinical Hypnosis Workshop.** UCI at Balboa Bay Club, Newport Beach. Thursday-Sunday. 30 hrs. $310. Contact: UCI (714) 833-5526.

May 2-3—**Providence Hospital Annual Spring Seminar.** Claremont Hotel, Oakland. Friday-Saturday. Contact: Medical Staff Office, Providence Hosp., 3100 Summit St., Oakland 94623. (415) 835-4500, ext. 2032.

May 3-4—**Holistic Medicine: The Pursuit of Wellness.** UCSF and State Dept. of Health Services at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: UCSF Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

May 10, 24—**Clinical Nutrition.** UCLA. Two Saturdays.

May 12-15—**Aerospace Medical Association.** Disneyland Hotel, Anaheim. Monday-Thursday. Contact: R. R. Hessberg, MD, Washington Nat'l Airport, Washington, DC 20001.

May 13-19—**Basic Diving Medicine.** UCSF at Fresno. One week.

May 14—**Deafness and Its Management.** LLU. Wednesday. 4 hrs. $30.

May 16-18—**2nd Annual National Symposium on Sexuality and Disability.** UCSF at Claremont Hotel, Berkeley. Friday-Sunday. Contact: UCSF Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

May 17—**Integrated Health Care.** Alameda-Contra Costa County Medical Assn. and UCSF at Kaiser Center, Oakland. Saturday. 6 hrs. $75. Contact: John B. Whalen, MD, 3300 Elm St., Oakland 94609. (415) 653-6320.

May 17-18—**Advanced Therapeutics in Clinical Nutrition.** St. Francis Memorial Hospital and American Society of Parenteral and Enteral Nutrition at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: Elena Tinloy, PharmD, St. Francis Mem. Hosp., P.O. Box 7726, San Francisco 94120. (415) 775-4321, ext. 3323.

May 18-23—**Fingers-to-the-Toes: An Orthopaedic Approach for the Family Practitioner.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Friday.

May 19-24—**7th Annual Family Practice Refresher Course.** UCLA and Santa Monica Hospital Medical Center at Sheraton-Miramar, Santa Monica. Monday-Saturday. Contact: UCLA.

May 21—**Frontiers in Clinical Genetics: Biology and Ethics.** General Hospital Ventura County at Casa Sirena and Lobster Trap, Channel Islands Harbor, Oxnard. Wednesday. 6 hrs. Contact: Harvey M. Harris, MD, Dept. of Med. Ed., Gen. Hosp. Ventura Co., 3291 Loma Vista Rd, Ventura 93003. (805) 654-3637 or 654-3638.

May 31-June 1—**Family Practice Symposium—8th Annual.** So. Calif. Permanente Medical Group at Marriott Hotel, Newport Beach. Saturday-Sunday. Contact: Catherine Andrews, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4516.

June 7-8—**Psychiatry for the Primary Care Physician.** UCLA. Saturday-Sunday.

June 7-8—**Nutrition: Myths and Realities.** UCSF and Institute for the Study of Human Knowledge at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

June 11-13—**Clinical Application of Hyperbaric Oxygen—5th Annual Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 24 hrs. Contact: G. B. Hart, MD, Dir., Baromedical Dept., Mem. Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801.

June 13-15—**American Medical Association Regional Meeting.** Hyatt on Union Square, San Francisco. Friday-Sunday. Contact: AMA, Dept. of Meeting Services, 535 N. Dearborn St., Chicago 60610. (312) 751-6503.

June 16-21—**Family Practice Refresher Course.** UCI at Marriott Inn, Newport Beach. Monday-Saturday. 50 hrs. $375. Contact: UCI (714) 833-5526.

August 10-14—**Western Hemisphere Nutrition Congress VI.** American Medical Association, American Institute of Nutrition, Nutrition Society of Canada, at Biltmore Hotel, Los Angeles. Sunday-Thursday. Contact: AMA, Dept. of Foods and Nutrition, 535 N. Dearborn St., Chicago 60610.

August 14-17—**Sexuality.** Orange County and American Urological Associations at Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

August 24-29—**Family Practice Refresher Course—8th Annual.** UCD at Del Monte Hyatt, Monterey. Sunday-Friday.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

May 1—**Child and Community Psychiatry—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

May 28—**Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday, 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

June 6-9—**Alaska State Medical Association Annual Meeting and Sports Medicine.** Mt. McKinley Village Lodge. Friday-Monday. Contact: Martha McDermaid, Alaska State Medical Association, 1135 West 8th Ave., Suite 6, Anchorage, AK 96501. (907) 277-6891.

June 19—**Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

MONTANA

April 16-18—**Office Gynecology—Univ. of Wash. Internal Medicine Review Sessions.**

April 16, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 17, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

April 18, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 18-19—**Montana Medical Association's 1980 Interim Meeting.** Helena. Friday-Saturday. Contact: G. Brian Zins, Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

May 7—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28-30—**Nuclear Medicine for Internists—Univ. of Wash. Internal Medicine Review Sessions.**

May 28, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 29, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

May 30, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 52 West Pine, Missoula, MT 59801. (406) 549-3782.

June 11-13—**Transient Ischemic Attack and Stroke; Seizure Disorders—Univ. of Wash. Internal Medicine Review Sessions.**

June 11, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

June 12, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

June 13, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

IDAHO

April 22—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

May 19—**Hypertension and Pregnancy—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 20—**Dysmorphology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony's Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

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MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

MEDICINE

April 25—**Endocrinology for the Clinician.** Portland. Friday. Jantzen Beach Red Lion Motor Inn. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

June 17-20—**American College of Physicians Review Course.** Portland, Tuesday-Friday. Jantzen Beach Thunderbird. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 25-27—**Symposium on Sports Medicine.** Eugene, Wednesday-Friday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

April 17-18—**Couples.** Seattle. Thursday-Friday. Swedish Hospital. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 18-19—**Tacoma Surgical Society Annual Scientific Program.** Tacoma. Friday-Saturday. Contact: Maxine Bailey, College of Medical Education, Pierce County Medical Society, 705 South 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

April 21—**Psychiatric Aspects of COPD and Depression in Chronic Disease.** Seattle. Monday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education & Training Dept., 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, Ext. 686.

April 24-25—**Respiratory Care.** Seattle. Thursday-Friday. Contract: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 24-25—**Interpretation/Management of Arrythmias.** Seattle, Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 25-26—**Anesthesia: Low Flow States—Pathology and Treatment.** Vancouver, British Columbia. Friday-Saturday. Four Seasons Hotel. Contact: Dr. K. Turnbull, Academy of Medicine, 1807 West 10th Avenue, Vancouver, BC V6J 2A9.

April 28—**Cardiomyopathies and Pericardial Disease—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 2-3—**Contemporary Clinical Neurology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 5—**Effective Alcoholism Treatment by General Physicians.** Seattle. Monday. Place to be announced. Copy of brochure available. Contact: Alcoholism Course, American Medical Society on Alcoholism, 733 Third Avenue, New York, New York 10017. (212) 986-4433.

May 5-6—**Patient-Physician Relationship.** Port Ludlow. Monday-Tuesday. The Admiralty. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 6—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Spokane). 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

May 8-10—**Washington Academy of Family Physicians—Annual Scientific Assembly.** Seattle. Thursday-Saturday. Red Lion Inn/Seattle-Tacoma Airport. 14 prescribed hours. Con-

tact: Carolyn M. Palmer, Washington Academy of Family Physicians, 3700 140th Ave., NE, Bellevue, WA 98005. (206) 883-8852.

May 12—**Principles of Antibiotic Therapy—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 16-17—**Controversies in Medicine.** Seattle. Friday-Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 16-17—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 19—**Ophthalmology Program.** Seattle. Monday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education & Training Dept., 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, Ext. 686.

May 20—**Hypertension and Pregnancy—Univ. of Wash. OB-GYN Sessions** (Spokane). 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 22-23—**Adolescent Medicine.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 30—**Ophthalmology in Family Practice.** Seattle. Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 5-6—**Physician/Patient Relationship.** Gleneden, Oregon. Thursday-Friday. Salishan Resort, Gleneden, Oregon. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 6-7—**Workshops in Musculoskeletal Disease.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Renal Disease.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 19-20—**Laboratory Medicine.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 23—**Basic Concepts of Immunology and Their Application—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

June 26-27—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 28-July 5—**Alaska Cruise—Emergency Medical Care: Trauma, Orthopedics and Surgery; Biomedical History.** 8 days. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

July 25-26—**Seafair II Anesthesia Meeting**—Washington State Society of Anesthesiologists. Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Sandra McDonald, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

April 16

SPONSOR: Cottonwood Hospital
TITLE: **Tumor Conference**
LOCATION: Cottonwood Hospital, Salt Lake City
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Carbon Hospital, Washington Park, Price 84501. (801) 637-1123
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84107 (801) 262-3461
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UU: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

April 17

SPONSOR: St. Mark's Hospital, Salt Lake City
TITLE: **Diabetic Retinopathy**
LOCATION: St. Mark's Hospital, Room G-304
FEE: None
CREDIT: 1 hour
CONTACT: Nellie Godfrey (801) 268-7003

April 18

SPONSOR: Hill Air Force Hospital
TITLE: **The Pregnant Patient and Management of Routine Non-Pregnant Problems**
LOCATION: HAFB Hospital Phys. Exam Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

April 18-19

SPONSOR: LDS Hospital
TITLE: **Calcium, Vitamin D and PTH Metabolism**
LOCATION: LDSH, 7th Floor Conference Room
FEE: $40.00
CREDIT: 10 hours
CONTACT: Barry Benowitz, MD (801) 364-3557

April 23-25

SPONSOR: VA Regional Medical Education Center
TITLE: **Heart Disease Update**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Lew Erschler (801) 582-1565, Ext. 1100

May 2

SPONSOR: Hill Air Force Hospital
TITLE: **Practical Application of Ultrasound and CT for the Clinician**
LOCATION: HAFB Phys. Exam Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

May 7

SPONSOR: University of Utah
TITLE: **Hematology/Oncology**
LOCATION: UU, Classroom D
FEE: None
CREDIT: 2 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

May 8

SPONSOR: University of Utah
TITLE: **Preceptor Teaching Skills**
LOCATION: Snowbird
FEE: To be arranged
CREDIT: 10.5 hours
CONTACT: Donna Harris, PhD (801) 581-8250

May 9

SPONSOR: Hill Air Force Hospital
TITLE: **Radiation Therapy of Skin Lesions**
LOCATION: HAFB Phys. Exam Room
FEE: None
CREDIT: 1 hour
CONTACT: Harold S. Jenson, MD (801) 777-3030

May 13-15

SPONSOR: VA Regional Medical Education Center
TITLE: **Substance Abuse**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Steve Harmon (801) 582-1565, Ext. 1100

May 21-23

SPONSOR: Ogden Surgical Society
TITLE: **35th Annual Medical Meetings**
LOCATION: Weber State College, Ogden
FEE: Members—no fee
Non-members—$10.00 registration fee
CREDIT: 25 hours
CONTACT: Ralph Foley, MD (801) 621-5400

May 23

SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—New Concepts in the Management of Congestive Heart Failure**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: 3 hours
CONTACT: Stan Everett (801) 350-1004

June 12-14

SPONSOR: Carbon Hospital, Price
TITLE: **4th Annual Castle Country Symposium**
LOCATION: Price
FEE: To be announced
CREDIT: 12 hours
CONTACT: Mary Louise Ghirardelli (801) 637-1123

June 16-19

SPONSOR: University of Utah
TITLE: **Physicians' Workshop on Alcoholism**
LOCATION: UU
FEE: $200.00
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

June 16-20

SPONSOR: VA Regional Medical Education Center
TITLE: **Legal Medicine**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Lew Erschler (801) 582-1565, Ext. 1100

July 11-12

SPONSOR: University of Utah
TITLE: **3rd Annual Birth Defects, Mental Retardation and Medical Genetics Symposium**
LOCATION: A. Ray Olpin Hall, University of Utah
FEE: $40.00
CREDIT: 13 hours
CONTACT: John Carey, MD (801) 581-8943

August 7-8

SPONSOR: VA Regional Medical Education Center
TITLE: **Geriatric Assessment**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Barbara Cordell, RN (801) 582-1565, Ext. 1100

August 26-28

SPONSOR: VA Regional Medical Education Center
TITLE: **Conflict, Confrontation, and Stress**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Alan Lundgren (801) 582-1565, Ext. 1100

September 11

SPONSOR: Rocky Mountain Center for Occupational and Environmental Health
TITLE: **Occupational Health for the 1980's**
LOCATION: Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-9, 1980, McKinley Village Lodge.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 23-27, 1980, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 24-27, 1980, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 13-17, 1980, Pacific Beach Hotel, Waikiki.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1980, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 2-4, 1980, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 16-18, 1980, MGM Grand, Las Vegas.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 7-9, 1980, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-31, 1980, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 30-October 3, 1980, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 2-5, 1980, Thunderbird at Jantzen Beach, Vancouver, WA.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 23-27, 1980, Snow King Inn, Jackson.

September 12

SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Medical Management of Ischemic Heart Disease**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: 3 hours
CONTACT: Stan Everett (801) 350-1004

September 22-25

SPONSOR: VA Regional Medical Education Center
TITLE: **Sexual Health**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: George Keiser, PhD (801) 582-1565, Ext. 1100

October 1-2

SPONSOR: VA Regional Medical Education Center
TITLE: **Geriatric Assessment**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Barbara Cordell, RN (801) 582-1565, Ext. 1100

October 16

SPONSOR: LDS Hospital (with Intermountain Thoracic Society, Utah Heart Association and University of Utah)
TITLE: **Postgraduate Course—Pulmonary Heart Disease**
LOCATION: LDSH
FEE: To be announced
CREDIT: 6 hours
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

December 12

SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Hypertension**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: To be announced
CONTACT: Stan Everett (801) 350-1004

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

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THE WESTERN Journal of Medicine

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CONTROLLING THE COST OF HEALTH CARE

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NEW ENGLAND JOURNAL OF MED
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The stress-secretion relationship in duodenal ulcer*

The best available evidence suggests that anxiety and emotional tension stimulate acid-pepsin secretion.[1] Also, the development of an ulcer crater in predisposed individuals, or the aggravation of ulcer symptoms, is often typically preceded by a stressful event or situation. *Anxiety* in particular seems to play a determining role in the course and prognosis of the disease, as well as its etiology.

A psychobiologic treatment

To obtain comprehensive relief, many duodenal ulcer patients need more than specific, acid-inhibiting medication—they also need dependable reduction of associated anxiety and emotional tension. With adjunctive Librax you can conveniently give your patient *both* clinical benefits from a single medication.

The pituitary gland plays a key role in the neurohormonal response to emotional stress, leading to an increase in gastric secretion.[2]

ROCHE

*Librax has been evaluated as possibly effective for this indication.

Please see brief summary of prescribing information on last page of this advertisement.

1. Isenberg J, Richardson CT, Fordtran JS: Pathogenesis of peptic ulcer, chap. 46, i *Gastrointestinal Disease*, ed. 2, edited b Sleisenger MH, Fordtran JS. Philadelp W.B. Saunders Company, 1978, vol. 1, pp. 800, 801.
2. Sun DCH: Etiology and pathology of p ulcer, chap. 27, in *Gastroenterology*, ed. edited by Bockus HL, *et al*. Philadelphi W.B. Saunders Company, 1974, pp. 579-

More than an antisecretory agent... acts on the entire disease entity

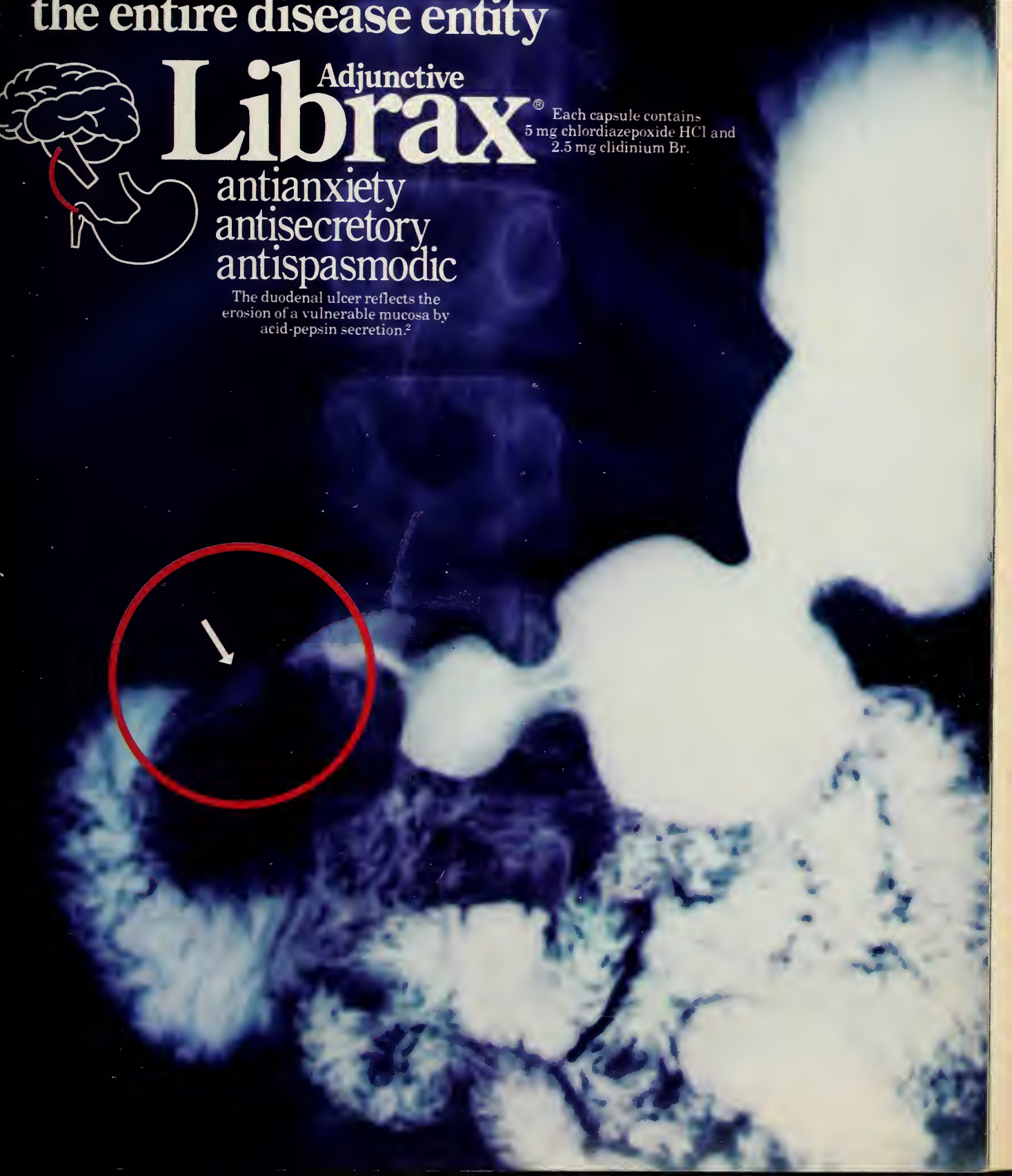
Adjunctive

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

antianxiety
antisecretory
antispasmodic

The duodenal ulcer reflects the erosion of a vulnerable mucosa by acid-pepsin secretion.[2]



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Adjunctive Librax®

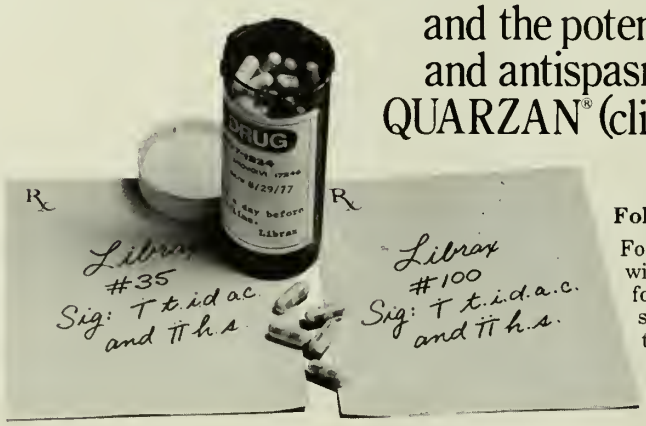
Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

The only duodenal ulcer therapy that provides the specific antianxiety action of LIBRIUM® (chlordiazepoxide HCl/Roche)

and the potent antisecretory and antispasmodic actions of QUARZAN® (clidinium Br/Roche)

Initial Rx

The initial prescription allows evaluation of patient response to therapy.



Follow-up Rx

Follow-up therapy with a prescription for a 2- to 3-week supply of medication usually helps maintain patient gains.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl/Roche) to known addiction-prone individuals or those who might increase dosage, withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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THE WESTERN Journal of Medicine

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(See Advertising Page 32)

★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the Utah State Medical Association and the Washington State Medical Association**

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THE WESTERN Journal of Medicine

Since 1902 (ISSN 0093-0415)

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Other factors must include:

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*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

1. Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

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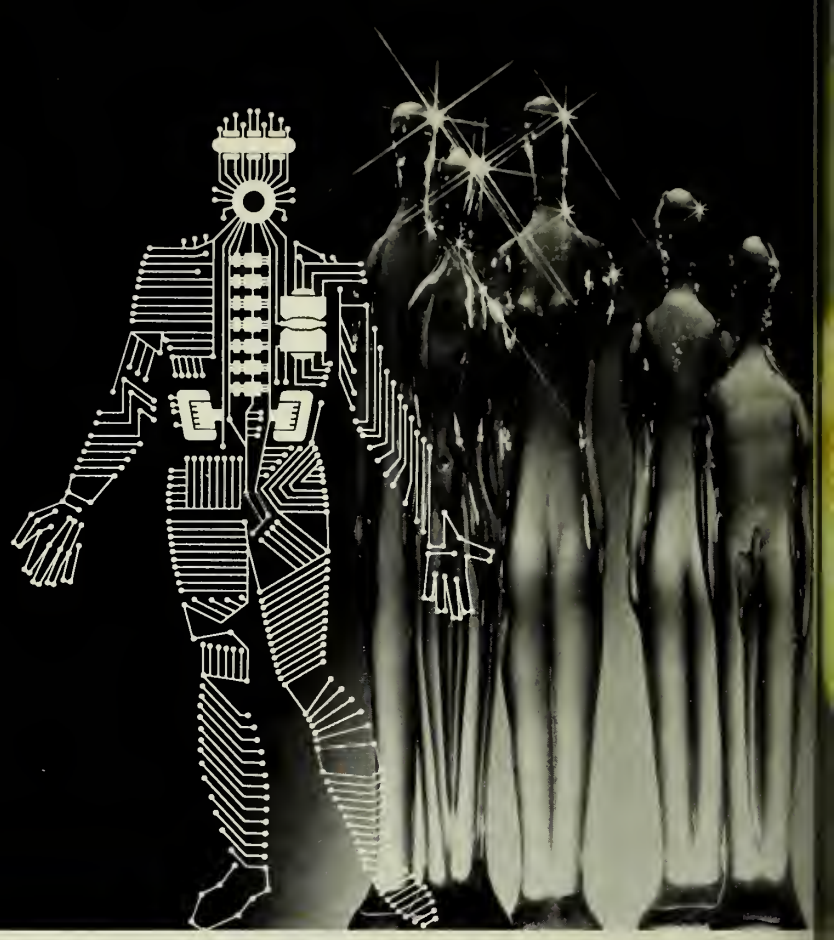

- No contraindications.
- Effective in all degrees of hypertension. It is mild to moderate in potency.
- Low incidence of depression, impotence, orthostatic hypotension—no fatal hepatotoxicity.
- Preserves kidney blood flow.

Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

The usual starting dose of Catapres is 0.1 mg at brea fast and 0.1 mg at bedtime. Some patients may bene from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg
Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1, 0.2, 0.3 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 mon longer.

Adverse Reactions: The most common reactions are dry mouth, drowsines sedation. Constipation, dizziness, headache, and fatigue have been rep Generally these effects tend to diminish with continued therapy. The foll reactions have been associated with the drug, some of them rarely. (In instances an exact causal relationship has not been established.) These in Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalit liver function tests; one report of possible drug-induced hepatitis without ic and hyperbilirubinemia in a patient receiving clonidine hydrochloride, thalidone and papaverine hydrochloride. Weight gain, transient elevation of glucose, or serum creatine phosphokinase: congestive heart failure, Rayn phenomenon; vivid dreams or nightmares, insomnia, other behavioral char nervousness, restlessness, anxiety and mental depression. Also rash gioneurotic edema, hives, urticaria, thinning of the hair, pruritus not assoc with a rash, impotence, urinary retention, increased sensitivity to alcohol, dry itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecom weakly positive Coombs' test, asymptomatic electrocardiographic abnorma manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished c sent reflexes and vomiting followed the accidental ingestion of Catapres (clon hydrochloride) by several children from 19 months to 5 years of age. G lavage and administration of an analeptic and vasopressor led to complet covery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-m intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) dosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0. (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000. available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.
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Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances, anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g., drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia, some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

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Why one benzodiazepine and not another?

Are you concerned about long-acting metabolites? Many clinicians, as well as pharmacologists, are beginning to draw attention to this problem (see New England Journal of Medicine, April 5, 1979).

In contrast to some older benzodiazepines, Ativan (lorazepam) does not give rise to long-lasting active metabolites. As with all benzodiazepines, you should follow the usual precautions concerning co-administration with other CNS depressants and warn your patients against operating dangerous machinery and motor vehicles.

However, it is noteworthy that Ativan showed no clinical evidence of accumulation even when given in high doses over periods up to 6 months. The half-life of free lorazepam is about 12 hours; steady-state serum levels are attained in 2-3 days. Comparable data for diazepam: 20-50 hours and at least 7-10 days. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Ativan has a convenient b.i.d. or t.i.d. dosage schedule; it is compatible with a long list of other medications and, of course, it is a highly effective anxiolytic agent, as established in numerous nationwide, double-blind, controlled evaluations in thousands of patients.

See important information on preceding page.

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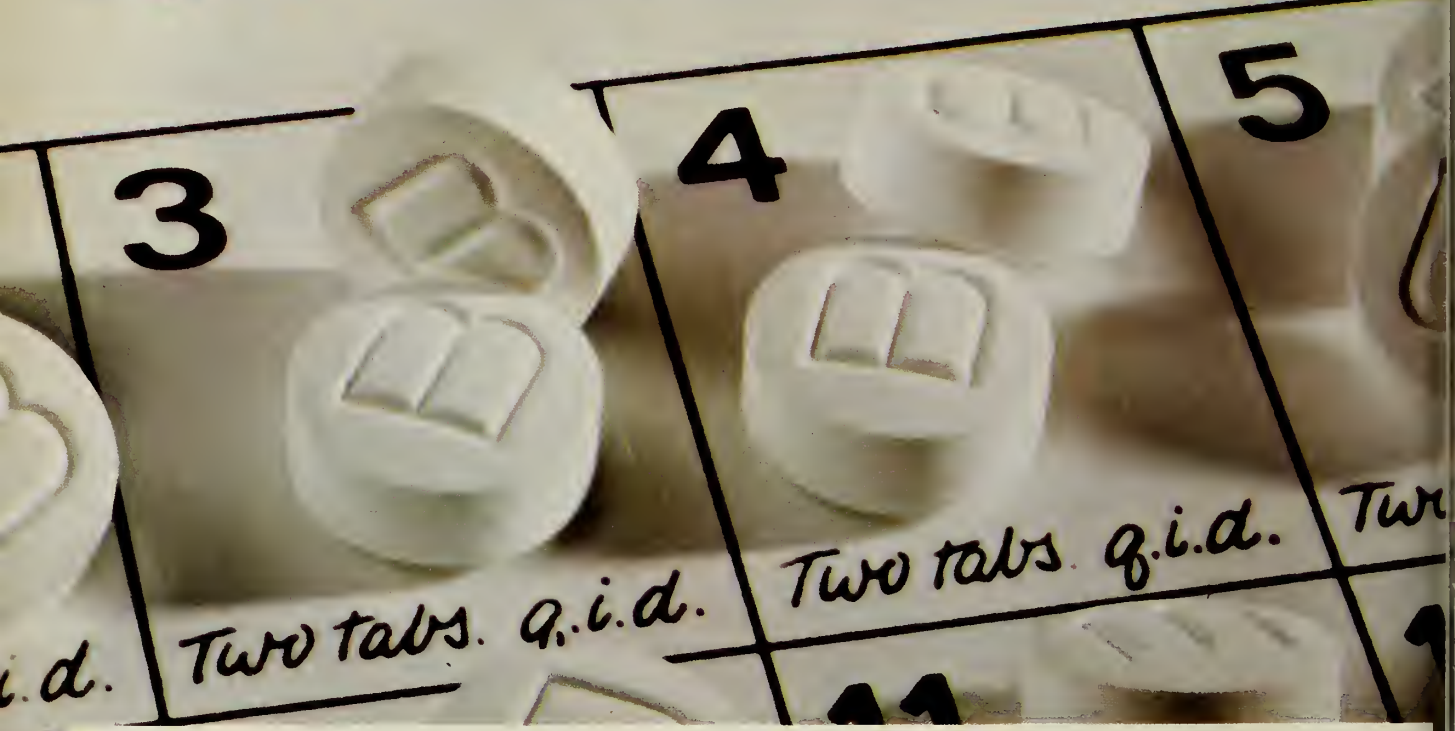

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Introduction

For 15 years national policies and polemics on medical care have centered on three concepts: cost containment, improved access and assurance of quality. This logical triad defines the three inseparable goals of any rational health policy. Although some groups in our society are dissatisfied with the quality of care, and although millions of patients and would-be patients are financially disenfranchised by current payment systems, the dominant theme of federal health policy has been "cost containment." It is likely to remain so well into the 1980's.

So much has been said, written and attempted in the name of controlling medical costs that the term is becoming a discredited buzz word. Yet it is difficult to find definitive and authoritative answers to some basic questions. What exactly are the policies and programs of the major national organizations? What are their rationales and underlying philosophy? How are these programs supposed to promote the public's interests? How do individual practitioners feel about cost containment? What has been learned through economic analyses of the medical cost problem? Is voluntarism winning or losing the fight against more government regulation? Are there any promising new approaches?

The symposium that follows is the result of asking national leaders and knowledgeable spokesmen to address these questions. It begins with the positions of the four major shapers and movers of medical care policies: the Health Care Financing Administration, the Blue Cross/Blue Shield Associations, the American Medical Association and the American Hospital Association. Next come two papers by hands-on practitioners, Dr. McGill and Dr. Donald. Together, they give us a look at the real-world dynamics that cost containment programs must take into account if they are to have an impact.

In refreshing contrast to most economists, Dr. Neuhauser has written a candid, personal statement, combining his grasp of technical cost issues with his understanding of the political process. Like most (but certainly not all) prognosticators, he sees competition as the probable best hope for restraining unnecessary cost increases. One unique form of competition is described by Dr. Moore. His "primary care network" may or may not be a forerunner of things to come. But the fact that such an unusual plan is in actual operation attests to the willingness of physicians to try by the private route an approach they would categorically reject if it were promoted by government.

Two voices are not heard in this symposium: a state government's and the public's. The former omission will be redressed in the next issue of the journal, which will carry a major policy statement by the California Department of Health Services on its Medicaid program (Medi-Cal). The latter omission reflects the prevailing doubt that there are spokesmen for the public's myriad attitudes and expectations. The conventional view is that the federal and state governments now speak for the public through elected political representatives and their appointees. Still, it is difficult to see how political debates and initiatives in cost containment have advanced the public's interests. This issue is taken up by Mr. Derzon, who proposes a new view of government's role in medical care and a new stance by private sector representatives in their relationships with government agencies.

This compilation should enable readers of the Western Journal to examine more critically their own attitudes, responsibilities and actions in eliminating unnecessary expenditures for medical care. At least three deductions emerge from the contents of the symposium. First, politicization of the cost issue has produced little besides distorted views of its nature and magnitude and questionable political benefits. Second, it is no longer possible to separate completely private and public sector responsibilities for costs, quality and access. Third, it is time to seek alternatives to adversary procedures in resolving policy differences if the individual persons and institutions that collectively comprise "medical care" sincerely intend to advance the public's best interests.

PAUL J. SANAZARO, MD
Symposium Editor

Meeting the Health Care Challenge: Improved Program Management

LEONARD D. SCHAEFFER
Washington, DC

The Health Care Financing Administration (HCFA) is the government agency that administers Medicaid and Medicare, and is responsible for standards and certification programs, and for Professional Standards Review Organizations. HCFA is attempting to improve program management, while securing the very best health care for the 47 million Medicare and Medicaid beneficiaries. Better management would allow resources to be focused where the greatest need exists and would thereby increase program effectiveness.

THE SURGEON GENERAL has reported that the health of the American people has improved significantly in recent years. The extent to which these improvements result from better and more accessible medical care rather than environmental or life-style changes is not known. However, the medical profession can clearly claim a good deal of credit. Unfortunately, while our general health has never been better, the cost of medical care has never been higher.

In 1978 health expenditures totaled $192.4 billion compared with only $74.7 billion in 1970. If we proceed as predicted, the nation could easily be spending over $368 billion by 1984 to secure health services. As the availability of better health care continues to increase so will the demand for more public financing of that care. In 1980 alone, the Health Care Financing Administration (HCFA) will serve some 47 million Medicare and Medicaid beneficiaries through the purchase of $47 billion worth of health services. This task is awesome and involves an obligation to our beneficiaries, providers, the Congress and the people of the United States.

The challenge is one of program management, which is intimately related to service delivery. Only by improving the management of our programs can we hope to improve on the delivery of health care services to our beneficiaries. Better management will allow us to focus our resources where the greatest need exists and thereby increase program effectiveness.

HCFA's basic function is to finance health care services, but its overriding goal is to secure the very best health care for those persons who rely upon the Medicare and Medicaid programs. We must depend on the physician—the decision-maker—to help make that happen. That dependence is graphically illustrated by the fact that 70 percent of all resource decisions in the health care systems are made by physicians.

Federal health care programs are entering the 1980's with extremely limited resources, with no excess dollars now and no expectations of having any extra in the future. Therefore, it is essential to make more prudent management decisions which will in turn make better use of our limited dollars.

There are three important challenges to our management expertise in areas which I know are of concern to physicians. First, we must find ways to simplify HCFA programs—make them more understandable to both the physician and the beneficiary.

Second, we need to take steps to make Medi-

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care and Medicaid more consistent with each other. Both are financing programs even though they were established for different social purposes and with somewhat separate target populations. Integrating Medicare and Medicaid wherever possible will make doing business with the government a good deal easier, thereby improving access to care for our beneficiaries. Third, we must make changes in our methods of operation to become more coordinated with the practices of the private insurance industry. The Health Care Financing Administration is moving ahead in these areas.

HCFA has spent a great deal of time, for example, reviewing the various procedure coding systems. When HCFA analysts began this review, they found more than 100 coding variations being used in Medicare and Medicaid. We have recently concluded that establishing a common system based largely upon CPT-4 (*Current Procedural Terminology,* 4th Edition, AMA) is the most suitable for our programs. In reaching this decision, we sought and received valuable assistance from many representatives of the health sector, ranging from the American Association of Health Data Systems to the National PSRO Council, as well as the American Medical Association (AMA).

HCFA will modify CPT-4 in two ways. First, we will expand CPT-4 to encompass other types of providers and, second, we will adjust as necessary to make it suitable for use in all care settings. As the modifications are being delineated, we will continue to have extensive consultations with the AMA components of the health care industry for review and comment on the prototype. By 1981 we expect to have the prototype ready for testing and evaluation to assess its ability to serve both reimbursement and medical records abstracting procedure labeling needs. Once these test results are available, probably near the end of 1981, we will discuss them with the AMA and other groups to assist us in judging the final product. If these efforts are successful, HCFA will begin implementing a single labeling system suitable for all our procedure information needs in 1982.

During the course of these developments, however, HCFA will not lose sight of our final goal: to approve and support only those conversions of carrier, state Medicaid agency or Professional Standards Review Organization (PSRO) procedure labeling systems that will be compatible with the use of the modified CPT-4; that is, CPT-4 Terminology of Physician Procedures, a five-digit basic procedure field, and one or more sets of two-digit modifier fields. In addition, by mid-1980 we expect a Notice of Proposed Rulemaking (NPRM) which will establish a requirement that all Medicaid programs use procedure labeling systems that have been approved by HCFA. We also plan to mandate the use of these standards as conditions for certification of Medicaid Management Information Systems. Medicare carriers and intermediaries as well as the Professional Standards Review Organizations will also have the modified CPT-4 requirements built into their contractual, grant or agreement stipulations.

Though all of this will take time, HCFA will persist in instituting a common labeling system because it is crucial to our efforts to simplify claims processing and improve the interface between Medicare, Medicaid and the PSRO's.

The AMA is to be commended for its willingness to negotiate and for its leadership on this issue. That organization's efforts have led to other organizations, such as the Health Insurance Association of America and the Blue Cross and Blue Shield Associations, signaling their support. However, while consensus on this issue is building, we still have not yet totally won the support of some very key groups such as the hospital medical records librarians. We plan on again meeting with these organizations in the very near future in the hope of reaching common ground, and we look to you for assistance in this effort.

However important we see the implementation of a common procedure terminology system, the concept is not without problems. There are those in the Department and in the Congress who have expressed concern that employing a new coding system in Medicare and Medicaid could result in an escalation of benefit expenditures. HCFA does not expect this to happen, but as a precaution we are experimenting in South Carolina to test methods of obviating this potential problem.

Results of these and other tests will be critical to our development of the final system, and we will vigorously address any impediments as they arise. Implementation of a modified CPT-4 system will not only substantially simplify our programs, but will also make the mechanics of dealing with the government much easier.

Another issue is the use of the common claim form. In my tenure as Administrator of the Health Care Financing Administration, I have heard many complaints from physicians and their office staffs alike that there are too many forms neces-

sary to claim reimbursement, be it federal or otherwise. Too many forms which ask for the same information about the same person. HCFA is now taking steps to help reduce that paperwork burden.

In the very near future we will begin a gradual phaseout of the current HCFA-1490 claim form. In its place we will utilize an HCFA-approved common claim form for Part B services. This claim form, based on one designed and developed by the AMA and the Health Insurance Association of America along with the Blue Cross and Blue Shield Associations, will suffice for all Medicare claims and most Medicaid claims, and will also meet the needs of the private insurance industry. A very similar form has already achieved widespread acceptance by physicians, and is being used by 12 Medicare carriers and 15 Medicaid claims processors, as well as 33 private insurance organizations. We see the advent of the common claim form to be yet another step toward overall simplification of Medicare and Medicaid while improving the interface between our programs and other third-party payers.

We plan to require the use of the common claim form for all Part B Medicare claims beginning in middle to late 1980. The conversion to the new form will be gradual to allow for the utilization of already printed HCFA-1490's. We do not intend to immediately mandate the use of this form in the Medicaid program because of the many different claims processing systems that exist. However, we will engage in consultation with the state on this issue and we look to the medical profession to urge acceptance of the form across the board.

However, the new common claim form will not be suitable for use by Medicare beneficiaries. Our Office of Beneficiary Services has met with many beneficiary groups to help develop a simplified short form HCFA-1490. Proposed revisions are being tested with individual beneficiaries, and the results of these deliberations should produce a much more understandable version of the 1490 which will promote self-filing.

Issues of claims reimbursement lead directly to issues of physician reimbursement. Historically, reimbursement has been the most talked about and the most sensitive of all our health care financing issues. There is no question that our present system of reimbursing physicians leaves much to be desired. It is confusing. It permits specialty and geographic reimbursement differences which many believe are unwarranted. It favors high technology, hospital-based medicine over office-based primary care. The present system also allows for Medicaid payments in certain states which may be too low to assure our program beneficiaries access to physician care and last, but certainly not least, it is highly inflationary.

Trying to grapple with all these problems has not been easy. HCFA welcomed the broad debate which has surrounded the topic of reimbursement, and as a result several options for reform have been suggested to us, including changes in the assignment provisions and fee schedules.

Some of the suggested options may appear to be easy solutions to problems in the current system, but I believe we must proceed with care. Changes of this magnitude could easily affect beneficiary access to care and provider participation. Therefore, we will ask the Institute of Medicine to provide a forum for further discussion of physician reimbursement reforms. The Institute will be asked to establish a dialogue with physician groups to address all facets of this most difficult issue.

We would like the dialogue to include looking at existing physician reimbursement methods and participation arrangements, both public and private, and the effect of the rate of reimbursement on access to care. The success of this effort will depend on support from all physician groups and we look to the AMA for definitive leadership.

The health care financing decisions that we make at HCFA affect not only our beneficiaries, but providers of service and the health care industry at large. It is essential that those involved in health care—its delivery, management and financing—participate in that decision-making process to the greatest extent possible. Only with these discussions can we ensure that our actions in both policy and operational matters exert a positive force on the health care system in general. HCFA has made a strong commitment to do just that. I intend to continue to share our activities with the medical profession and look forward to the very necessary ongoing dialogue we must share if our goals to improve service to our beneficiaries are to be reached.

The Many Elements of Cost Control

WALTER J. McNERNEY
Chicago

For Blue Cross and Blue Shield Plans, cost containment is not a new concern but an activity that has been carried on for years. It has now been given new emphasis by the urgencies of inflation and the new focus of national attention on health care costs as one of its more conspicuous phenomena—chiefly a result of the inflation but often mistaken for, and mislabeled as, a cause.

BACK IN THE 1930'S, when the prepayment plans for hospital services were still so new that the name Blue Cross had not yet been invented, the concern for cost was already in evidence. The charge for a hospital inpatient day at the time was $6 to $8 in city hospitals and half that in the smaller communities, but the early Plans were aware of the need for controls and doing what they could to create them. The degree of sophistication of hospital accounting in that era may be indicated in a story told by one of my associates who was involved in the prepayment movement almost from the beginning. As a means of introducing the subject, if not the exercise, of cost control, one of the Plans had hired a CPA whose firm had done hospital audits to present a series of lectures on cost accounting methods for hospital administrators. When the idea was proposed to the local hospital council with the thought that it might wish to cosponsor the lectures with the Plan, the council president, a retired clergyman who was administrator of one of the city's major hospitals, objected. "I don't see why we have to worry about all these details," he said. "Either you're going along all right, or you aren't going along all right, and that's all there is to it."

Actually, of course, it was a lot more complicated than that even then. While the Plans kept up the effort to modify rises in health care costs, it must be acknowledged that cost control was not a high priority objective during the 1950's and 1960's. These were decades of proliferating specialization in medical practice and corresponding growth of medical technology. Public expectations of what medicine could accomplish were rising; hospitals expanded to meet the growing demand, and Blue Cross and Blue Shield Plans kept pace. It was during these years of prosperity, too, that industry was building plants and adding employees, unions were increasing in size and power, and health care benefits became a standard provision of collective bargaining agreements. Thus it was a time characterized by expansion and the beginning of inflation, yet it was also a time when regional planning of health care facilities was introduced, and some Blue Cross Plans were bold enough to tie hospital reimbursement to approval by the appropriate voluntary regional planning authority. It was also a time when the first studies of hospital and physicians' services utilization were undertaken, many of them financed by Plans, and when the first utilization committees were organized by physicians on hospital medical staffs. It was a time when Blue Cross Plans and hospitals undertook trials of prospective reimbursement and budget review; tissue committees were developed into full-scale medical audits; Blue Shield Plans introduced physician profiles, and the "usual, customary and reasonable" fee system was born. It can be argued that none of these measures proved to be effec-

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tive in stemming the swift currents of expanding demand and rising prices. That is true. But it should not obscure or diminish the fact that it was the voluntary system, and not government, that introduced the planning, reimbursement and utilization controls that are now seen as the chief bulwarks of the cost containment effort. And the fact is that while planning, utilization review or reimbursement practice by itself influences but does not control cost, these measures applied together consistently over time, and in recent years supplemented by shifts in Blue Cross and Blue Shield benefit patterns to encourage use of less expensive outpatient services, have had a cumulative effect that is reflected in Blue Cross and Blue Shield experience.

Progress in Cost Containment

A recent ten-year review of inpatient hospital utilization, for example, indicated that hospital admissions, inpatient days and length of stay for all Blue Cross subscribers had declined greatly. Hospital admissions were down 5.7 percent in 1978 compared with 1969; length of stay declined from 7.3 to 6.4 days, or 13.1 percent, over the same period, and the number of inpatient days per 1,000 Blue Cross subscribers dropped from 896 to 729, an 18.6 percent reduction. At the same time, hospital outpatient visits by Blue Cross subscribers increased significantly, unquestionably reflecting the expansion of benefits by most of the Plans to include payment for outpatient services, ambulatory surgery, and preadmission testing. Changes of this magnitude obviously have multiple causes, but it seems likely that the emphasis on cost containment in the past several years has resulted in changing attitudes and changing behavior among physicians, as they have become increasingly aware of the cost problem and the impact of their decisions on cost experience.

Preliminary evidence, derived from a sample of eight Plans, shows that the reduction in patient days per 1,000 subscribers in those Plans was associated with a reduction in elective admissions and a reduction in length of stay for acute admissions. Both events suggest that the cost containment efforts of Blue Cross were paying off. Also, it would appear that the Voluntary Effort to cut down the rate of growth in health care costs, sponsored by the American Medical Association, American Hospital Association and Federation of American Hospitals, in which the Blue Cross and Blue Shield Associations have been supporters and participants from the beginning, has helped physicians and other providers of care understand the impact on medical practice of arbitrary limitations on hospital expenditures such as those proposed in the federal administration's "cost cap" legislation. Proposals that were seen initially by some physicians as simply an effort to put the squeeze for greater efficiency on hospital management are now widely understood to constitute a threat to medical practice. Inevitably, arbitrary limits on hospital expenditure would result in restrictions on the physicians' freedom to order procedures and services for their patients.

We could get cost cap legislation, of course, but the chances that this will happen have been diminished by the Voluntary Effort, as well as by all the planning, utilization and reimbursement practices that have been gaining momentum over the years. These were all initiated by the voluntary sector, but it would be less than honest not to acknowledge that they have been speeded on their way—and in some places energized—by such measures as the Planning Act, Professional Standards Review Organizations (PSRO's) and the persistent prodding of the Health Care Financing Administration. This has been a not only appropriate but probably necessary distribution of responsibility between government and the private sector, with each doing what it does best and what the other cannot do. Thus, the voluntary sector can innovate and manage better than government; while the government can regulate and set standards and insist that they be met—things the private sector cannot do.

Sometimes the lines are not so easily drawn. PSRO's have been an attempt by government to set standards and insist that they be met in the effort to control utilization that had its beginning in the voluntary sector when Dr. E. A. Codman began his reviews of the care of surgical patients at the Massachusetts General Hospital in 1913. Soon afterward, Dr. Codman became one of the initiators, with Dr. Franklin Martin, of the American College of Surgeons and its hospital standardization program, which evolved into the Joint Commission on Accreditation of Hospitals in 1952. These were all efforts to safeguard the quality of patient care, and it was not until PSRO's were established by the Medicare Amendments of 1972 that quality assurance was combined with

a cost containment objective—in the minds of some of the amendments' congressional sponsors if not in the language of the law itself. But the cost saving dimension of quality assurance was not created *de novo* in the 1970's. It had been observed by Dr. Codman, and it was not unnoticed in the periodic wars on unnecessary surgery initiated by the American College of Surgeons when Dr. Paul R. Hawley, who had been a Director of the Blue Cross Commission, was director of the College in the mid-1950's.

Medical Necessity Project

Cost saving was a prime objective but quality was an important consideration throughout development of the Blue Cross and Blue Shield Associations' Medical Necessity Project, which has been worked out with the cooperation of the American College of Surgeons, the American College of Physicians, the College of American Pathologists and several other specialty societies. The project has been developed in three phases up to now. In the first phase, 42 surgical and diagnostic procedures were identified that the appropriate specialty societies agreed could no longer be considered useful. Once agreement was reached on the procedures, the Associations recommended that Blue Cross and Blue Shield Plans should notify physicians and provider institutions that payment for them would no longer be made in the absence of specific instruction from the attending physician in each such instance. In the second phase the Associations and the professional societies determined that routine diagnostic tests for nonsurgical admissions to hospitals—the familiar "admissions batteries"—should be paid for only when specifically ordered. Following additional specialty society consultation, this policy was later extended to include surgical admissions as well. A third phase, announced early this year, named a number of additional procedures that were judged to be obsolete, not clinically useful or reliable, or lacking in scientific evidence to support their effectiveness.

"There are doctors who are still ordering or performing procedures long since discredited," Dr. Marvin Shapiro said recently, explaining the Medical Necessity Project to a group of physicians and health insurance executives at a national conference. "Since the third parties in general ask nothing more than that there be a physician's order and evidence that the procedure was performed, virtually all these services are being reimbursed. I believe that by reintroducing into the patient-physician relationship an element which has largely been lost, some very impressive savings can be achieved. The additional factor is that of the physician's concern, and the patient's concern, for the direct cost to the patient."

If the patient and physician were both aware that a contemplated procedure was not likely to be paid for by a third party, and would certainly not be paid except by specific report, explained Dr. Shapiro, a practicing radiologist and former chairman of the board of California Blue Shield, "the contemplated procedure would be considered in quite a different light than it is now. In all probability there would be a discussion involving the potential benefit to the patient. The physician would be largely free of the pressure which depends to a great extent on the existence of insurance. If authoritative professional opinion had stated that the procedure was indicated only in special situations not included in the case being considered, the physician would also be largely relieved of peer pressure and fear of malpractice action. A dramatic decrease in useless services could be anticipated, with great saving and with much improved quality of care."

In separate actions following careful study with the indicated specialty societies, the Associations have now recommended more than 100 procedures for which Blue Cross and Blue Shield Plans should make payment only when the physician specifically justifies the case. Because the Plans have had to initiate educational programs for their participating physicians and hospitals, and in some cases introduce new language in Blue Cross and Blue Shield contracts, it will take time before these still new policies can take universal effect. Thus we have hesitated to make estimates of the amounts that may be saved, but obviously the potential must be calculated in the hundreds of millions of dollars. And we are banking on the fact that more selective testing and ordering of procedures will result in better diagnosis and treatment. As Dr. Robert Moser, executive vice president of the American College of Physicians, has said, "The policy is based on sound medical practice. It is often the less secure, less thoughtful, less up-to-date physician who orders the routine battery, taking the shotgun approach as opposed to the more targeted rifle approach. Good medical practice just happens to be more economical." The Blue Cross and Blue

Shield Associations view the medical necessity program as an ongoing effort. We hope next to deal with the repetition of tests before and after hospital admissions and with increased emphasis on appropriateness of the site of surgery.

Hindsight suggests that if it is indeed true that physicians have been ordering unnecessary procedures for years, either from habit or because they figure they might pick up an occasional aberration that way and "it doesn't hurt anybody because the insurance pays the bill," then the Medical Necessity Project, or something like it, should have been initiated years ago—and not just in 1977 and 1978, when cost containment had become a necessary and familiar objective. The argument is logical enough, but experience with many of the earlier efforts to control utilization suggests that had any such proposal as the Medical Necessity Project been introduced much before our time, it would have been seen as an unacceptable invasion of the individual physician's freedom to control every aspect of patient care, and as such it would have met with aroused opposition on all sides, instead of the thoughtful cooperation it has evoked from the specialty societies. Until cost containment did become a necessary and familiar phenomenon, the medical culture not only subordinated considerations of cost to considerations of patient care, which was and is and will remain the proper thing to do in every individual case, but generally regarded considerations of cost as irrelevant to patient care, if not actually improper in the true professional environment. It has taken a virtual revolution of values in medicine, brought on by the inflation that is threatening established values in every segment of the society, to move cost up to where it can be seen as an element of the patient-physician relationship and indeed, as we have seen, as a component of quality. The Medical Necessity Project, like lines of cars at gas stations, is peculiarly a product of this time.

Cost Containment Membership Standards

Also peculiar to this time, and unlikely to have been practical much earlier, are the cost containment membership standards for Blue Cross and Blue Shield Plans, now a requirement for their affiliation with the national organizations. The standards evolved over time from formal commitments to health care cost containment strategies that were applied systematically beginning in 1973. They were adopted by both the Blue Cross Association and the Blue Shield Association in 1977 in response to private market pressures, before consolidation of the staffs of the associations the following year. The standards themselves are simple: "A Plan shall adopt and implement a cost containment program," they state. "Such program, incorporating those guidelines established by the Board of Governors, shall include a means to analyze relevant data concerning costs of health care, to make appropriate recommendations as to effectiveness, and to submit reports as required to the Association." For Blue Shield Plans, for example, the "core requirements" that each Plan must have either implemented or planned for implementation at a specific date include an active program of fraud and abuse investigation; an active program of post-payment utilization review, using both technical and professional screening, as appropriate; educational programs stressing prevention of unnecessary and inappropriate use of health care services and unnecessary administrative costs for individual subscribers, groups and providers; active coordination and subrogation of benefit programs, aimed at restricting Plan liability or payment for services already provided or paid for in other programs, such as workers' compensation or other insurance; a local data base on health care delivery, including means to analyze data and compare them to national experience; a program of public information about the Plan's progress and role in cost containment, and a program providing restraints on the rate of escalation of the customary range of charges with evidence of specific physician commitment.

In addition, each Blue Shield Plan is expected to have implemented or to be actively developing optional cost containment activities that make sense in its environment. Depending on Plan size, these may be such innovations as ambulatory surgical facilities or second opinion surgery programs; new financing mechanisms such as diagnosis-related payment; cost-directed administrative initiatives in data processing, profile analysis, or payment procedure; educational programs for providers or subscriber groups aimed at improving utilization experience, and "any other innovative program that has a reasonable possibility of being effective in the cost containment effort," as it is stated in the forms Plans complete for current renewal of their Association membership.

The Blue Cross Association membership stan-

dard has 12 specific requirements, designated as structural and programmatic. Four of the structural requirements are concerned with planning and evaluation of Plan cost containment programs and have to do with maintaining and analyzing cost and utilization data; establishing cost containment objectives and action plans to achieve them, and implementing systems for evaluating progress. A fifth structural guideline requires the Plan to report cost containment results annually to the Association. The program guidelines deal with fraud and abuse; coordination and subrogation of benefits; systems for verifying eligibility for subscriber benefits and billing for noncovered services; claims utilization review for determination of medical necessity and appropriateness of care; participation in planning activity; subscriber and provider education, and "periodic exploration of incentive approaches for paying participating hospitals." Like the Blue Shield guidelines, the Blue Cross standard also lists additional activities in which many Plans are already engaged and those that are not are urged to get moving, notably including negotiation of medical necessity and health planning provisions in Plan hospital contracts, concurrent review, planning and developing Health Maintenance Organizations (HMO's) and shared services. "Overall, the cost containment approval standard and guidelines provide a context within which Plan management can strengthen the effectiveness of existing programs and develop new programs where appropriate," says the cost containment manual that was distributed to the Plans in 1977 and has been updated periodically.

Energy Management

There has scarcely been time as yet to get another cost containment activity into the standard —the energy conservation program or "energy management," as we like to call it—that now involves an estimated 60 percent of all the Plans. This began in 1975, when Blue Cross of Greater Philadelphia funded a study in six Philadelphia hospitals to identify energy problems and develop a systematic approach to energy conservation. This resulted in publication of a manual, *Practical Energy Management in Health Care Institutions,* that had wide distribution all over the country and led to a follow-up program in cooperation with the Delaware Valley Hospital Association, including 58 hospitals in the Greater Philadelphia area. With the help of business and union representatives, energy audits were conducted in all the hospitals, and no-cost or low-cost changes, rather than remedies involving major capital investment, were instituted. For a total cost of $1.6 million, the program brought about annual energy cost savings of $6 million, or 15 percent of total annual energy expenditures in the participating institutions.

As these results became known, Plans in Pittsburgh, New Jersey, New York, New England and elsewhere followed the Philadelphia lead and a national cooperative effort was initiated with a grant from Exxon. Assistance was provided by the Hospital Research and Educational Trust, an affiliate of the American Hospital Association. Last year, in a program coordinated by Blue Cross and Blue Shield of Greater New York, the seven Plans in New York state made $4 million in low-interest loans available to the state's 250 eligible hospitals to cover the cost of energy audits and match federal grants for technical assistance. The loans are expected to stimulate programs that will cut hospital energy costs in the state by 12 percent. Similar programs are operating across the country, with a savings potential that has been estimated at $500 million a year.

Cost Awareness and Competition

For the long term, it seems likely that the greatest economies of all—though it may not be possible always to package and quantify them, like energy savings—may be achieved through the continuing effort to make cost a component to be considered a proper part of every patient-physician transaction. While individual hospitals, Blue Cross and Blue Shield Plans, and some medical societies initiated a few such programs in the past, physician awareness of the cost of patient care decisions has been a primary goal of the Voluntary Effort during the past two years, and the number of programs has been increasing rapidly. In a survey conducted last year, more than half the responding Blue Cross and Blue Shield Plans said they had "cost awareness" activities scheduled, usually presentations at hospital medical staff and medical society meetings. Those that were judged to have been most successful, invariably, were those that had been planned with and presented by physicians.

For interested Plans and institutions the Blue

Cross and Blue Shield Associations have produced a film, "The Buck Stops Here," which has now been shown to several thousand physicians at such meetings, and most of the programs have emphasized the importance of showing the film and presenting or sponsoring classes for medical students and house staff. But the most effective demonstrations are those prepared and presented by local physicians for their own colleagues, using data from their own practices and showing how their own hospitals and practices will be constrained, inevitably with a dampening effect on the quality of patient care, unless the cost escalation can be curbed by carefully tailored and locally sensitive action.

Among government officials, lawmakers, economists, businessmen, and some physicians and health care administrators, there has been a growing number in the past year or two who believe that the alternative to regulation is not just voluntary cost containment but the promotion of competition in the market for medical services. Of course, there has always been competition for patients and for patronage among physicians and among institutions, but for the most part it has been competition based on competence and service, not price. What is sought now by many of those who would introduce what they see as system reform is frank price competition, so that the employer, and ultimately the individual consumer, would have a choice of competing health care plans, and the plans in turn would thus have an incentive to bid low prices and cut down cost. The competitive model usually is the Health Maintenance Organization concept, and it is envisioned that employers would give employees a choice between the present health insurance arrangement and one or several HMO's, with the employer contributing the same amount in each case and the employee thus presumably given the incentive to choose a low-cost plan. In another version, consumers would simply be given "health care vouchers" that could be applied toward purchase of health care services, and left free to shop around in the open market—a plan resembling the school voucher proposal that surfaced briefly in a few states in the early 1960's, sponsored by critics who were convinced the public school systems in their states were costly and inefficient.

Certainly it would be desirable if stronger incentives to reduce costs could be made to work in the market for health care services as they do elsewhere, and if a competitive model could be captured that would achieve this result and forestall the onrush of more, and more restrictive, regulation. It seems likely now that enough people are convinced enough that it can be done so that it will be tried in one form or another. But there are some complexities here that may have been overlooked by some of the enthusiasts for system reform. One is simply that there are not enough HMO's to go around. After a half dozen or more years of intensive promotion of the prepaid group practice concept by government and others, the number has increased from a few more than 100 to about twice that many, and it is estimated that it would take as many as 2,000 to provide a realistic choice of health care financing methods for a major segment of the population.

More than half the Blue Cross and Blue Shield Plans have either sponsored or are affiliated with HMO's in their territories, but experience with them has not been uniformly good; people generally like the idea of comprehensive, inclusive services at a fixed annual fee, but when it turns out that it means changing doctors or seeking service at new and often inconvenient locations, as is sometimes the case, they often decide to keep their existing health insurance, or switch back after a trial run. Some HMO's fail, often because of weak management or marketing skills. The result is that except in areas like Minneapolis, and the West Coast states so well covered by Kaiser facilities and services, and three or four others where new HMO's have been springing up in response to the new pressures for alternative models, employers either cannot offer a choice at all or the choice is so limited as to be generally unattractive. Thus, despite the attractiveness of the option, the most optimistic projections suggest that the number enrolled in HMO's, now less than 10 million, might at best be doubled in the next five to ten years, still far short of providing the kind of competitive thrust that could be expected to have an impact on cost.

Meanwhile regulation marches on, most recently with a proposal from the Health Care Financing Administration to accomplish by fiat what the Congress failed last year to accomplish by legislation—a cap on hospital revenues to be applied by establishing Medicare payment ceilings for Medicare services. Moreover, it is plain that if one or another of the "system reform" bills should be passed by the Congress in an effort to

inject competition into the marketplace, in the interest of equity it would have to include some kind of subsidy to encourage the formation of new HMO's where none existed, and a whole new generation of regulation would thus be introduced. So the hoped-for reform could turn out to be an invitation for more rather than a substitute for the regulation we already have. Finally, if these speculations should prove to be wrong and events should move more rapidly along the lines foreseen by the advocates of unlimited price competition in medical care, and institutions and groups start bidding against one another for employers and patients, some safeguards would obviously need to be established to protect the quality of the services. Neither an employer seeking bids on specified services for his employees nor a consumer shopping around with a health care voucher would be in a position to judge whether or not a low bid meant a cut-rate service. It is hard enough for utilization committees and PSRO's to make judgments of quality; for employers and consumers it would be impossible, and the Medicaid experience has shown that there are providers of service ready to take advantage of the unwary. The way things are going, we shall probably have more competition for medical services than we have had in the past, but it will not be—and should not be—unrestrained competition. At least, the consumer must be protected against a bad choice.

Personal Responsibility for Health

For the past half dozen years, there has been a growing public awareness of the many influences on health that lie outside of what we commonly consider to be the jurisdiction of the health professions and institutions. Heredity, the physical and social environment, and especially personal habits and behavior may readily have more to do with health status than medical care has, and realization that this is the case has resulted in a new emphasis on public health and environmental medicine, as well as visible changes in life-styles. The jogging phenomenon is the most obtrusive of these, but notable changes have also occurred in dietary habits and public attitudes toward smoking and drinking as more and more people have become convinced that they must assume greater responsibility for their own health. The rising interest of industry in the health of workers is indicated not only in the desire to hold down the costs of employees' health benefits but also in many new health maintenance programs offering screening to identify poor health risks and training, counseling or referral for treatment as indicated.

It seems clear now that these are not fads but evidence of cultural change, toward realization that no matter what we do about health care costs we shall need a more realistic view of prevention and health education than we have had in the past. In the new era envisioned in these activities there is a critically important role for doctors and hospitals. Patient counseling, the information content of care that has often been elided in a technological age, is a rising demand. In a recent public opinion survey, more than 70 percent of respondents said they considered their own doctors and hospitals the most reliable sources of information on matters related to health, but more than half reported that they received less information than they wanted and needed from these sources and turned instead to friends and neighbors, newspaper and magazine articles, and television programs—a circumstance that is not likely to improve the health status of the population. What could improve health status and at the same time offer what may be the best hope of containing health care costs for the long term would be an awakened interest in wellness on the part of physicians and their institutions. We have made a good start, but there is a long way to go to achieve a proper balance of curative and preventive medicine—and it may be harder to do even than it will be to achieve a proper balance of regulation and competition.

As carriers, Blue Cross and Blue Shield Plans are on the line. We are working with primary and secondary schools in encouraging life-time sports; cooperating with industry in associating selective diagnoses with work sites; developing screening benefits at work sites for such conditions as hypertension, alcoholism and drug abuse, obesity and cancer; paying for health education in hospitals, and beginning to examine the possibility of offering employers lower rates if they institute health promotion programs. In the last analysis however, the goal cannot possibly be accomplished without the thoughtful understanding and sustained interest and effort of physicians, working in partnership with employers, employees, other community groups, and individuals and carriers at the local level—close to the unique problems inevitably involved in achieving the proper balance.

Medicine's Role in Health Care Cost Containment

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During the 20th century, medicine has confronted a series of problems threatening health care delivery in the United States. Historically, crises developed related first to quality of care, later to access and finally to the current issue of cost. Factors responsible for the large increases in health care expenditures in the United States during the last decade include increased medical care costs, population and demand for care. Additionally, economy-wide inflation, advanced medical technologies, an aging population, the growth of health care facilities, expansion of third-party payment systems including Medicare and Medicaid and rising incomes per capita have occurred. Programs now exist, and others are being planned, through which physicians, individually in private practice and collectively through organized medicine, may confront this major challenge now threatening the very foundations of health care delivery in the United States.

DURING THE PAST DECADE, major public attitudes toward the American medical care system have shifted dramatically. In the era following World War II, the predominant emphasis was on improving access for all Americans to quality health care. However, when asked what they considered to be the major problem facing medicine in the United States today, a large majority of public respondents cited cost-related issues.[1] This concern is not unique to the public; the cost issue now dominates *physician* attitudes toward medical care as well.[2]

As a result of this increased attention, the recurrent question from all sectors of the health system is simply "What is to be done?" The purpose of this paper, therefore, is to address methods whereby the individual physician and organized medicine as a whole can confront the cost problem. The emphasis is on programs designed to (1) reduce rates of increase in the price of various resources combined to produce medical care and (2) slow the rate of increase in the quantities and types of care demanded by patients.

Initially, the background of the cost issue is examined. After a historical perspective is developed, various causes of spiraling costs are identified. Finally, specific strategies for reducing medical expenditures are presented and discussed. These include initiatives currently in operation, as well as programs now under discussion that offer promise for the future.

Historical Background

In recent years, much has been written concerning the quality-access-cost triad in the American medical care system. It has become clear that each of these three issues must be considered in the context of the two remaining elements. In historical perspective, however, the relative emphasis on each of the three components has changed substantially during the 20th century.

Quality

At the turn of the century the *quality* of medical care delivered in the United States was of primary concern to the nation in general and to

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organized medicine in particular. This increased attention to the quality of medical care was in direct response to the pervasiveness of incompetent practitioners who purchased medical degrees from unaccredited medical education programs. It was during these early years that medicine took major steps toward formalizing the medical education process and standardizing the quality of care delivered. Many of the American Medical Association's (AMA) current activities in professional review and accreditation may be traced directly to this era.

Access

Following World War II there was an increasing emphasis on *access* as a potential problem in the health care system. Initiatives from a wide range of sources were directed at expanding the supply of health care facilities. As a result of both public and private mechanisms, access to care improved dramatically during the postwar period. For example, between 1948 and 1971 the Hill-Burton Act provided 30 percent of the total funds spent for hospital modernization and construction.[3] The increase in the number of nonfederal, short-term general hospital beds from 330 beds per 100,000 population in 1950 to 450 per 100,000 in 1977 is largely attributable to this program.[4]

During the early 1960's, the federal government, with encouragement from organized medicine, significantly increased its financial support of medical education. The number of medical schools increased from 79 in 1950 to 122 in 1978; the number of medical graduates rose from 6,135 to 14,393 over the same period.[5] This increased emphasis on the education of health professionals was responsible, in part, for a rise in the number of physicians per 100,000 population from 144 in 1950 to 201 per 100,000 population in 1978.[6]

In addition to the availability of sufficient resources to provide adequate levels of care, access depends upon the public's ability to pay for needed care without suffering severe financial strain. In response to this need a major expansion of private and public insurance programs for financing medical care developed during this period. According to the Department of Health, Education and Welfare's Health Care Financing Administration, "third parties" paid 67 percent of all personal health care services in 1978, compared with 35 percent in 1950. Medicare and Medicaid, in 1978, financed over $44 billion, or approximately 26 percent of all personal health care.[7] The fact that by 1973 members of low income families were using more physician visits per person per year and more hospital care than members of middle and high income families provides additional evidence of progress toward removing barriers to health care.[8]

The level of certain health indicators rose concomitantly with these major increases in care accessibility during the postwar period. The expectation of life at birth rose from 68.2 years in 1950 to 72.8 years in 1976. In 1950 for each 1,000 live births 29 infants failed to survive to one year of age. However, by 1978 infant mortality dropped to less than 14 deaths per 1,000 live births.[9,10] During these same three decades, treatments were discovered that all but eliminated poliomyeletis, tuberculosis and smallpox.

Cost

In the last five years the emphasis on problems of access has rapidly given way to major concerns about the *cost* of medical care. In one sense the very existence of the cost problem is a reflection of success in removing barriers to care access. However, it is now clear that the magnitude of the cost issue may threaten many of the earlier gains that resulted from constructing a system that provides quality health care to the American population.

Briefly, the magnitude of the cost problem can be described as follows. The Health Care Financing Administration reported that in 1978 total United States health care expenditures equaled $192.4 billion, an increase of more than 1,400 percent from the $12.7 billion dollar spending level in 1950. Health care consumed 9.1 percent of the United States gross national product (GNP) in 1978, compared with only 4.5 percent in 1950.[4]

If left unchecked at the current rate of increase, health care expenditures would consume approximately 13.1 percent of the gross national product in 1990. Current and projected levels of expenditures on health care clearly warrant careful analysis of the factors responsible for this cost spiral and the development of strategies designed to reduce medical costs to a socially acceptable level.

Factors Contributing to the Medical Care Cost Increase

Table 1 breaks down the 1950-1978 increase in total United States health care expenditures

into three components: (1) increases in the price of medical care delivered, (2) increases in the population and (3) increases in the quantity and type of care delivered per capita.[4]

Medical Care Prices

The increase in medical care prices is clearly the most important factor, accounting for 59.3 percent of the total increase in health expenditures. More than half of this price increase, however, is attributable to the general rate of inflation during the same period. In fact, evidence suggests that the costs of goods and services used by health care facilities and physicians to produce health care services generally increased more rapidly than the overall measure of the price of consumer goods, the Consumer Price Index (CPI).

Population Growth

As indicated in Table 1, growth in the United States population, per se, during the 1950-1978 period accounts for only approximately 10 percent of the increase in the country's health expenditures. However, changes in the *composition* of the United States population over time have influenced substantially the demand per person for both the quantity and type of medical services delivered.

The Demand for Medical Care

Table 1 indicates that a substantial proportion of the increase in health expenditures (31.1 percent) is explained by increased demand per person in the quantity and type of services purchased by patients. A number of factors underlies this increase in per capita demand for health care services. These include changes in the composition of the country's population, a trend toward increased use of hospital care, the public's increasing perception of health care needs, growing household incomes and the growth of health insurance coverage. Additionally, demand increased due to the development of sophisticated procedures and treatments stemming from new advances in medical technology which made previously untreatable illnesses treatable.

In terms of shifting population composition, the United States population has aged considerably during the last three decades. In 1950 persons 65 and older constituted 8.1 percent of the population; in 1978 this group made up 11.0 percent of the population.[11] Because elderly persons use substantially more hospital days per person than others, this population change affects the demand for medical services and, therefore, health care expenditures.[12]

Increased per capita health care spending is not distributed equally among various health care services and commodities. For example, in 1950 physicians' services accounted for 21.7 percent of each health care dollar; by 1978 the physicians' services share had fallen to 18.3 percent. Concomitantly, hospital care rose from approximately 30 percent to almost 40 percent of the total during the same period.[7]

This shift in the relative allocation of health care dollars reflects a general trend toward increased demand for hospital services, as measured by days-of-care per 1,000 population, although recently this increase has slowed. Conversely, the number of visits to physicians' offices, per person per year, has remained relatively stable during the last 15 years. This change has had major impact on total health expenditures because of the high relative cost of hospital inputs in care delivery.

Insurance and other health care financing mechanisms also influenced the type and quantity

TABLE 1.—*Factors Contributing to the Increase in Personal Health Expenditures in the U.S. for Selected Calendar Years: 1950-1978**

Sources of Increase	*In Billions of Dollars (Percentage Distribution Shown in Parentheses)*				
	1950-65	1965-71	1971-74	1974-78	1950-78†
Medical care prices‡	10.9 (41.5)	19.0 (54.7)	13.6 (47.3)	49.6 (74.0)	93.1 (59.3)
Population§	5.3 (20.0)	3.3 (9.5)	2.1 (7.2)	4.4 (6.5)	15.1 (9.6)
Quantity and quality increase (per capita)	10.2 (38.5)	12.5 (35.8)	13.1 (45.5)	13.1 (19.5)	48.9 (31.1)
TOTAL¶	26.4 (100.0)	34.8 (100.0)	28.8 (100.0)	67.1 (100.0)	157.1 (100.0)

*Source: Center for Health Services Research and Development, American Medical Association. Chicago.
†For the entire period, 1950-1978, the dollar increase is the sum of the increases for the interim periods.
‡Prices are consumer price indexes (CPI-U) with 1967=100.
§Population is total population in the United States and possessions including armed forces and federal civilian employees overseas and their dependents, in millions (Source: Gibson RM[7]).
¶Total refers to changes in total personal health care expenditures for the indicated calendar years (Source: Gibson RM[7]).

of health care demanded. Whereas total per capita personal health care spending increased over tenfold between 1950 and 1978, direct or *out-of-pocket* expenses rose only five times during that period.[7] Thus, to a certain extent, insurance shielded consumers from feeling the full economic effect of increased health care spending. Indeed, it has been argued that because insurance reduces the out-of-pocket costs of health care, it increases patient demand for medical services.

Insurance mechanisms also influence the nature and the price of the services utilized. Third-party coverage traditionally has been most complete for care rendered in hospitals. For example, in 1978 third parties paid over 90 percent of the nation's total hospital bill, but covered only 66 percent of expenditures for physicians' services.[7] This coverage encourages the use of relatively cost-intensive institutional care. It has also been suggested that hospital price increases are related to third-party payors' use of cost-based reimbursement to institutional providers.

In summary, the major components accounting for recent increases in total health expenditures in the United States are increases in the price of medical inputs and increases in the quantity and type of care delivered. Each of these components may potentially be influenced by the individual physician in daily practice and by organized medicine through policy and program formulation. However, it must be emphasized that the success of any cost-containment strategy, given the complexity of this issue, will require concerted effort and extensive cooperation from many sectors influencing health care delivery. Further, it is the professional responsibility of physicians, individually and collectively, to ensure that any cost-containment program will maintain both the quality of and access to care delivered.

Strategies for Containing Medical Care Costs

Due to an increasing awareness of the cost issue, the American Medical Association realized the need for a coherent and unified framework within which to structure cost-containment activities. In 1975 the National Commission on the Cost of Medical Care was impaneled by the AMA for this express purpose. This independent commission, composed of persons from the full spectrum of groups interested in health care, developed a comprehensive report which continues, at present, to have a major impact on the policies of organized medicine. The full content of this report is discussed elsewhere and will not be recounted here except as it pertains specifically to input price and demand containment.[13] However, it is important to note that major portions of the Commission's activity involved an extensive fact-finding effort which now provides the foundation for a wide range of cost-containment programs.

After 18 months of deliberation, the Commission issued an extensive report which contained 48 recommendations for initiatives designed to confront the cost problem. These recommendations are categorized into four general areas: (1) marketplace for medical care, (2) demand for care, (3) supply of medical services and (4) technology.

The Commission examined two basic approaches for confronting the health care cost issue: strengthening price consciousness and increasing use of public-utility type regulation. After considerable debate, the Commission came to believe that an approach that coupled increased competition in the health care sector with voluntary restraints based on provider and patient understanding would have the greatest success in slowing the cost spiral.

The Commission represented a significant development for two reasons: (1) it focused physician attention on the need for health care cost awareness and (2) it also emphasized the need for a broad coalition of interested parties to develop and implement cost-containment strategies. Many of organized medicine's present cost-containment programs directed at input price control reflect the work of this influential body.

Programs to Contain Input Prices

The major component of the large increase in total health expenditures in the United States during the last two decades has been the increased price of medical inputs delivered. Therefore, cost-containment strategies should include methods through which individual physicians and organized medicine can influence the price of medical inputs.

Voluntary Fee Restraint

Discussion of input price control invariably leads to the issue of physicians' fees. Public groups, business leaders and government agencies are often quick to criticize physicians and organized medicine for failure to moderate fees. However, the record on this issue is clear.

The AMA has encouraged and supported the

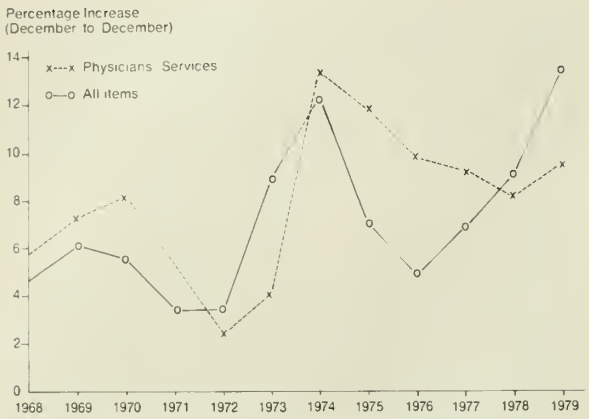

Figure 1.—Percentage increase in all-items and physicians' services components of the Consumer Price Index, 1968 to 1979 (source: Bureau of Labor Statistics).

successful effort of individual physicians to moderate their fee increases. The Association strongly supports a policy, reaffirmed by the immediate past president of the AMA, Tom E. Nesbitt, MD, calling for voluntary fee restraint. In 1978, CPI data indicated that physicians' fees rose 8.1 percent, compared with a 9.0 percent increase in the all-items index.[14] In 1979 all items rose 13.3 percent; by comparison, however, the index for physicians' services increased only 9.4 percent (see Figure 1).

Figure 1 also indicates that between 1973 and 1978 the price of physicians' services increased at a rate higher than that for the all-items CPI component. However, this comparison is misleading if the trend in physicians' office *expenses* is not also considered. Despite a relatively stable volume of visits produced by the average physician per year, practice expenses increased 87 percent between 1970 and 1977, while the CPI all-items index rose only 56 percent during the same period.[15]

This suggests strongly that even during periods when the price of physicians' services increased more rapidly than the CPI, these increases were not generating higher net incomes for physicians. Rather, they appear to reflect adjustments in price caused by increased practice expenses. Data collected by the AMA's Center for Health Services Research and Development support this position. The data show a 5.8 percent annual increase in physicians' average net income from medical practice between 1968 and 1978. During the same period, the all-items index of the CPI rose an average of 6.5 percent annually. As a result, the typical physician's *real income,* or purchasing power, declined 0.67 percent per year, on average, from 1968 to 1978. (Trends in Physicians' Fees, Patient Visits, and Physician Income. Unpublished data, AMA, Center for Health Services Research and Development, 1979.)

In perspective, it appears that individual physicians have responded and will continue to respond to the call from organized medicine to voluntarily restrain fee increases in a direct attempt to slow rising health care costs.

The Voluntary Effort

Another major program to contain increases in medical input prices involves a number of organizations. In November 1977 the American Medical Association, together with the American Hospital Association and the Federation of American Hospitals, initiated the Vountary Effort for Health Care Cost Containment (VE). Since that time, organizations representing health care manufacturers, insurors, business, local government and consumers have joined this effort to control medical costs. The VE's goals include a reduction in the annual rate of increase in total community hospital expenses; a narrowing of the difference between the rates of increase of community hospital expenses and the GNP; and further moderation in the rate of increase in the prices of physician and other health care services relative to the rate of increase in the CPI.

The evidence, thus far, supports progress by the VE toward meeting these goals and offers promise for the viability of voluntary sector initiatives as effective cost-containment programs.

The National Commission on the Cost of Medical Care

A third major thrust from organized medicine to generate strategies designed to contain medical input costs is reflected by recommendations of the National Commission on the Cost of Medical Care (NCCMC). These included (1) sharing by physicians of diagnostic findings, (2) strengthened support for peer review of care delivered and fees charged and (3) development of programs to reduce malpractice insurance premiums and thereby reduce fees for medical procedures.

Additional Programs

The AMA has developed and widely disseminated a variety of materials designed to aid physicians in monitoring and evaluating their own fees and expenses in individual practices. For

example, the AMA's Center for Health Services Research and Development publishes a monthly *CPI Report* which is distributed to executives of state, local and specialty societies, and which is available upon request from the Center. This report provides timely analyses of the prices of physician and other health care services in relation to prices in other segments in the economy. The Center also annually surveys a sample of office-based physicians concerning their practice patterns, professional expenses, incomes and fees. Information from this survey is published in the Center's annual publication, *Profile of Medical Practice*. In addition, the AMA developed and disseminated to 335,000 physicians a simple technical assistance guide designed to teach physicians how to monitor changes in their own fees and expenses.

The above discussion of programs designed to contain medical input price increases is not intended to be exhaustive. Rather, its purpose has been to highlight the major types of strategies being developed in this critical area.

Programs to Contain Increased Demand for Medical Services

The second major component of the medical cost problem, increased demand, has generated intensive discussion in recent months. The controversy concerns the extent to which individual physicians influence patients' decisions to seek medical care. In strict terms, physicians' services constitute only 18 percent of total national health care spending, and only 21 percent of personal health care spending.[7] Thus, there is a real limit to the impact on total health care costs which can be realized simply by physicians limiting their practice expenses. It has been suggested, however, that physicians greatly influence the type, quality and quantity of most health care services a patient receives, and, therefore, actually control 70 percent to 80 percent of personal health care expenditures. (Trends in Physicians' Fees, Patient Visits, and Physician Income. Unpublished data, Chicago, Center for Health Services and Development, AMA, 1979.)

Cost-consciousness Among Physicians and Patients

Clearly, the extent of any physician's influence varies greatly from patient to patient and according to case severity. The fact that, on average, physicians influence between 21 percent and 80 percent of total health expenditures should not detract from the essential point that *physicians and patients together determine the quantity and type of care delivered and therefore both groups must become more cost-conscious for any program to be successful in controlling total health expenditures*. It is for this reason that organized medicine has developed and is currently exploring strategies designed to educate physicians and the public on the cost impact of various medical treatments.

Physician and Public Educational Programs

In this regard, the National Commission on the Cost of Medical Care, described earlier, called for intensive efforts to develop public health education programs and to make physician information available in the form of easily obtained regional physician and hospital directories.

Programs to create and expand courses and seminars on the socioeconomics of medical practice in both undergraduate and graduate institutions have also gained a wide range of support from organized medicine as well as other groups in the health care sector. These efforts should generate a greater understanding of the relationship between treatment and cost among physicians.

The Importance of Out-of-pocket Costs

Education, in isolation, cannot be expected to slow demand for medical services if current financial incentives are not restructured. Even informed patients, when there are no out-of-pocket costs, have incentives to increase demand for care unnecessarily. It is for this reason that insurance arrangements which reintroduce cost sharing on a limited basis have been suggested as potential strategies for general cost-containment. These include both co-insurance and deductible arrangements which protect patients from catastrophic illness but require some out-of-pocket payment for less severe episodes.

While patient participation in the financing of health care is desirable, extreme care must be taken to avoid structuring incentives for either physicians or patients which unduly limit access to needed medical care. Nor should physicians practice medicine from a cost-minimization viewpoint. Medical care should be demanded by patients and delivered by physicians with an adequate understanding of cost consequences. Educational programs for both consumers and

providers of care similar to those advocated by the National Commission on the Cost of Medical Care will provide major impetus toward this goal. In addition, the restructuring of financing arrangements to include some direct out-of-pocket costs, while retaining strong catastrophic coverage, should reduce unnecessary physician visits and thus have a positive effect on cost reduction.

Conclusion

The 20th century has witnessed a major evolution of medical care delivery in the United States. The historical record shows medicine's ability to confront pressing problems and resolve them successfully. Initially, extensive efforts were directed toward improving the quality of care delivered; later, this focus shifted to the expansion of access to care for all Americans. However, the challenge of the cost problem is greater than any preceding it. Physicians, individually as well as collectively through organized medicine, must respond quickly and successfully to this challenge or risk the loss of freedoms within which medical care has always been delivered in the United States. The problem is complex, as must be its solutions. However, through strong leadership and reasoned initiative, the medical profession must once again show its willingness to confront this major crisis in health care.

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The Hospital's Perspective on Cost Containment

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Cost containment has long been a concern of hospitals and the American Hospital Association (AHA). In recent years, however, cost containment has assumed a special prominence in hospitals, becoming both a political and social necessity. The hospitals' and AHA's activities in cost containment fall into four major categories: first, the Voluntary Effort to Contain Health Care Costs, of which AHA is a founding partner; second, administrative effectiveness; third, capital effectiveness, and, finally, medical effectiveness. Some programs to promote administrative effectiveness are shared administrative services, energy conservation, careful attention to staffing patterns and management effectiveness review. Capital effectiveness involves technology assessment and other means of deciding how to make the most of the hospital's dollar. Medical effectiveness can be accomplished by such methods as medical audits, utilization reviews and shared clinical services.

COST CONTAINMENT by any name—"efficiency," "savings," "balancing the budget"—has long been a concern of hospitals and the American Hospital Association (AHA). In recent years, however, cost containment has assumed a special prominence in hospitals, becoming both a political and social necessity. In view of this, there has been an active effort in the hospital field to seek new approaches and methods to contain costs.

Hospitals' and AHA's activities in cost containment fall into four major categories which will be discussed in this article. They are, first, the Voluntary Effort to Contain Health Care Costs; second, administrative effectiveness; third, capital effectiveness, and, finally, medical effectiveness.

Voluntary Effort

Recognizing the need for a comprehensive cost containment program that would consider quality and accessibility issues, AHA, in 1977, joined with the American Medical Association and the Federation of American Hospitals to form the Voluntary Effort (VE). The key to the VE's success is its coalition nature; it is an effort which includes, in addition to hospitals and physicians, business, Blue Cross and Blue Shield, commercial health insurance carriers, suppliers and consumers.

The long-term goal of the Voluntary Effort is to narrow the gap between the rise in health care expenditures and the rise in the gross national product. The National Steering Committee of the VE selected the gross national product as an appropriate measure because, as it rises, it reflects both inflation and real growth. Health care expenditures are also a measure of inflation and real growth, in the form of increased utilization and increased service intensity. Increases in health care expenditures cannot, and should not, be compared with increases in the Consumer Price Index, which is a measure of inflation alone. Ignored is the fact that expenditures also rise when more people need health services or when a new, much-needed diagnostic procedure is introduced in hospitals.

Health care costs have always grown faster

Refer to: McMahon A: The hospital's perspective on cost containment, *In* Controlling the cost of health care—A symposium. West J Med 132:399-403, May 1980

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Reprints not available.

than inflation and must continue to do so if accessibility and quality of care are to continue to improve.

VE's First Two-Year Goals

As a first step toward achieving a closer and more consistent relationship between the rise in health care costs and the increase in the gross national product, the Voluntary Effort National Steering Committee stressed hospital cost containment.

Hospital expenditures have received much attention in the drive to reduce health care costs for two reasons. Hospital expenses are 40 percent of total health expenditures and are therefore highly visible. Second, hospitals have been the target of federal legislative and regulatory proposals to contain costs, such as the Carter Administration's proposal to place a limit on hospital revenues.

The first VE hospital cost containment goal called for a two-year four-percentage-point decrease in the rate increase in hospital expenses. This goal was set in 1977, when hospital expenses were increasing at a rate of 15.6 percent. By 1978, hospital expenses were increasing at a 12.8 percent rate, or 2.8 percentage points slower than the year before, ahead of schedule for meeting the challenging target.

When the VE set the 11.6 percent goal, inflation was 6.6 percent. By 1979, however, inflation was increasing at a pace greater than 13 percent, pushing up wages and the prices hospitals pay for goods and services twice as fast as foreseen in 1977. Despite this and an increase in utilization, the VE continues to show encouraging results. During 1979 expenditures increased 13.4 percent. Adjusted for the higher-than-expected inflation, hospital expenses would have increased 11.7 percent, an increase consistent with the goal of the Voluntary Effort. The VE has shown that strong private-sector leadship in cost containment can effectively control increases in expense, even with high inflation and a sharp increase in utilization.

The Next Phase

Voluntary Effort goals and objectives for 1980 and beyond mark a maturing of the VE. Three priorities direct the scope of programs and activities of the VE: (1) cost containment and cost-effectiveness in all sectors of the health care industry, (2) an increased emphasis on the role of all National Steering Committee members and (3) an emphasis on balancing the issues of cost, quality and accessibility, in order to develop long-range cost-effectiveness as well as short-range cost containment.

The National Steering Committee has reaffirmed its goal to achieve a closer and more consistent relationship between total health care expenditures growth and total gross national product growth. The hospital cost target calls for the national increase in total inpatient community hospital expenditures to decelerate by 1.5 percentage points from 1979, providing the overall inflation rate does not increase. The numerical goal focuses on inpatient community hospital expenditures, rather than total hospital expenditures as in previous years. The change in emphasis concentrates hospitals' voluntary efforts on their most expensive services and on the services which have the highest cost-saving potential. VE goals also call for a stable hospital bed census and an attention to the growth of full-time equivalent employees in hospitals.

VE contributions from all members of the coalition are important in achieving the long-range cost-effectiveness goals. Health promotion and illness prevention, industry consultation with government on proposed health care regulations and legislation, and public education require the support of all the VE partners and of the community outside the health care system.

Physician-oriented VE goals call for voluntary restraint of fees and physician participation in voluntary utilization review programs. Manufacturers and suppliers are again being asked to exercise restraint in pricing policies and to support voluntary cost containment programs. The VE coalition has asked insurance carriers and other purchasers of care, such as public and private concerns, business and organized labor, to examine payment systems, incentives and consumer demand. Purchasers will look for methods to decelerate demands for costly services and to extend preventive and primary care benefits. Other members of the VE coalition, particularly physicians and hospitals, must work with these partners to suggest ideas, support change, and inform patients and colleagues about the benefits of changes in the reimbursement system.

Hospital-based Programs for Cost-Effectiveness

As a founding and active member of the Voluntary Effort, AHA and its member hospitals have

actively developed cost containment programs. Hospital administrators and trustees have developed a wide variety of cost-effective approaches to health care in their hospitals.

Although many of these programs do not affect directly the medical staff, physician understanding of and cooperation with these cost-effective measures promotes a unified, cost-conscious health care attitude within the hospital.

Administrative Effectiveness

Hospitals provide the physical plants, treatment facilities and equipment that give physicians a place to deliver medical care. In addition, they employ the skilled personnel who operate the medical equipment and who provide nursing and therapeutic care for patients. Administrators and governing boards have experimented with ways to reduce increases in hospital expenses for providing these services, and at the same time provide high quality services to physicians and to the community. Some of the methods hospitals are using include shared administrative services, energy conservation, careful attention to staffing patterns and management effectiveness review.

Hospital participation in shared administrative services has increased rapidly as hospitals take advantage of sharing in order to lower per-unit costs. The 1979 American Hospital Association's Shared Services Participation Profile indicated that of 5,742 hospitals surveyed, 80.1 percent participated in some form of shared administrative or clinical service.

Group purchasing is the most frequently used administrative shared service, with purchases including dietary items, drugs, intravenous solutions, linen, medical and surgical supplies, and other products. Group purchasing has been proved to be a moneysaver for hospitals, providing them economies of scale and increased bargaining power with suppliers. Other commonly shared administrative services are data processing, education and training, laboratory services, biomedical and clinical engineering, and credit unions.

Energy has become the second largest budgetary expense in some hospitals, and anticipated rapid price growth will make energy conservation increasingly important. Energy in hospitals is used for physical plant heating and cooling, food preparation, laundry, lighting, and medical and surgical services, among others. Treatment and testing is often energy-intensive.

To assist hospitals in conserving energy, AHA and the AHA-affiliated Hospital Research and Educational Trust are conducting an Exxon-funded study on energy management in hospitals, and AHA has supplied hospitals with information and management studies.

Much energy can be saved by projects that leave health care treatment areas untouched. Computerized energy control, recaptured heat from laundry areas, and other maintenance-oriented energy-saving programs are saving hospitals money without impinging on patient care. Other programs, such as scheduling use of treatment facilities to most efficiently use energy, require support from a hospital's medical staff.

Efficient use of a hospital's staff contributes to efficient use of health care dollars. Personnel is the largest single expense for hospitals, and one of the ways the Voluntary Effort steering committee suggested hospitals could meet their cost containment goals was by restricting the growth of full-time equivalent employees. Approaches to this include admission scheduling, cross-training of technicians, innovation in staffing patterns, and redesign of work flow. All of these staff changes take into account quality of care as well as economy considerations.

AHA is also involved in projects designed to increase administrative and other staff effectiveness. Educational sessions and seminars sponsored by AHA and its affiliated societies often stress methods and motivation for cost-effective and management effective health care.

In addition, AHA has developed a management analysis tool, the Program for Institutional Effectiveness Review (PIER), to involve an entire hospital, including the medical staff, in evaluating hospital performance. PIER's self-evaluation questions and answers help hospitals assess their overall strengths and weaknesses, and improve departmental relations and communications. The program looks at five interlocking components of hospital management: institutional, financial, patient and clinical, human resources, and materials and facilities. PIER aims at identifying problem areas and improving operations to help hospitals provide the best possible health care delivery environment.

Hospitals have used these and other approaches to administrative effectiveness to maintain a quality health care environment and to meet the VE goals of cost containment and cost-effective health care.

Capital Effectiveness

Hospital cost containment policies must consider the effect of long-range building and equipment plans on a hospital's plan to keep down health care costs. There are always demands from the community and from the medical staff for new equipment and services. There are always more dollar requests than the hospital can supply funds. With cost restraints on hospital expenditures, hospital boards must look closely at each equipment or service request. They must spend limited capital to produce the greatest effect on the health care needs of the community.

Recognizing the need for sophisticated technology assessment, AHA created a program, Technology Evaluation and Acquisition Methods (TEAM), designed to give hospitals a structure and a procedure to evaluate these requests. Overall, it provides a dollars-and-cents financial analysis and a patient use projection for services or equipment. TEAM helps the decision-makers identify how a proposed purchase or service would be used; whether the hospital would use the service or equipment enough to justify its expense; whether the service or equipment would duplicate other existing community services, and what the advantages and disadvantages of the technology or clinical service would be. TEAM guides the requesting physician or department in thinking through the request and alternatives and in looking at the impact of the equipment or service on the hospital staff and other services. TEAM analyses can also be used to support a request for a certificate of need before a state planning board.

Through TEAM and other means of technology assessment, hospital administrators and physicians can cooperate to support the best patient care at the same time they avoid underutilized, overlapping technological and clinical services. TEAM is one method to assure capital effectiveness.

Medical Effectiveness

Physicians have played an important part in the Voluntary Effort—from steering committee representation, to resolutions, to answering a call from the American Medical Association to restrain fee increases below the rise in the Consumer Price Index. Physicians, serving as the medical staff of a hospital, have a primary opportunity and a primary responsibility to help hospitals keep down the rise in their expenditures.

A hospital's medical staff should take part in medical audits and utilization review as a means of ensuring cost-effective care. Physicians must also keep cost-effectiveness goals in mind when treating their patients. Assessing standing orders for tests, reexamining treatment methods to secure medically effective care at a lower price and prescribing the appropriate level of care—such as outpatient surgery or home care—are several ways that physicians can advance both the good of their patients and cost-effective health care.

Another approach to medical effectiveness is the sharing of clinical services, in addition to the administrative services mentioned earlier. Many hospitals now share blood banks, radiology services, and laboratory and pathology clinical services. Other hospitals look for cost savings and efficiency by sharing a burn care unit, obstetrics, physical or occupational therapy, and anesthesiology. Some clinical services work better in a sharing arrangement for some hospitals than for others, depending on relative location, cooperation and need.

Saving for the Future

In the health care field health information is recognized as an important means of raising the health status of the community and, in the long run, diminishing the need for costly care for advanced medical conditions. Hospitals in some communities provide classes, public service media programs and other health promotion activities. Screening programs designed by hospitals in conjunction with community organizations or local business can help detect illness in its early stages, allowing referral to a physician for appropriate and early care.

Physicians can help assure the success of these hospital efforts by offering their time and skills in developing information and programs, and by encouraging these programs as a positive way to bring patients who need medical attention and health care information into the health care system.

Hospitals and medical schools have begun preliminary work in cost awareness programs for physicians, students and the general public. Some hospitals keep their medical staff aware of procedure costs by providing physicians with a daily print-out of the hospital bill for a sampling of

their patients; others have physicians review costs periodically. Medical schools are incorporating cost information into their program—pointing out that the most expensive and the most technologically advanced services do not necessarily serve a patient best and orienting students to think of alternatives.

Cost Control and Quality Care

The many health care cost containment projects now under way in hospitals and other health care institutions affirm that cost-effective care and quality care are not mutually exclusive goals. Hospital administrators and governing boards are seeking new ways to involve physicians in finding and developing these cost-conscious ideas because both hospitals and physicians are concerned with the same final goal: high quality, effective health care in their communities.

Summary

Overall, the AHA and hospital perspective on cost containment encourages methods for providing high quality care while meeting the demand for lower cost growth. AHA and its member hospitals have concentrated on meeting the goals of the Voluntary Effort and on improving administrative, capital and medical effectiveness in hospitals.

Hospitals consider their efforts to bring the increase in health care costs into a closer relationship with the rise in the gross national product a part of their responsibility to the community and to other segments of the economy. The Voluntary Effort has heightened hospitals' traditional awareness of cost-effectiveness. Cost-effectiveness will remain an integral part of a hospital's mandate and of American Hospital Association programs.

What Price Government Regulations?

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Cost containment in health care will be a major target for governmental regulation in the coming decade. A number of potential economies in health care exist, among them a reduction of the heavy burden of government regulation. It is important to review pending congressional action as related to health cost, as well as congressional proposals for reform of the regulatory agencies. Organized medicine is involved in cost containment and the private sector has made some progress. However, there is much that individual practitioners can do.

WE ARE BEING TOLD by medical economists and political prognosticators that cost control will be the major thrust of governmental regulations in the 1980's. That was not the original plan, but the current political crisis in the Middle East and an economy-minded Congress would seem to preclude large federal spending programs such as National Health Insurance. Instead we will see an even greater emphasis on economy in health care—"more efficient delivery systems," avoiding expensive duplication, learning to do more with less, and on and on, ad nauseam. Of course what this really means is that somewhere in our governmental superstructure regulation must be placed on the rising costs of health care, regardless of how well justified those costs may be.

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We all know the litany. The combined cost of all health services adds up to about 9 percent of the gross national product—too much, we are told. I have often wondered just who it is that decides how much is too much, and on what basis. To bring this 9 percent figure into focus I think we should also recognize that the combined cost of government accounts for 22 percent of the gross national product and government employs 17 percent of the population. How much is too much government?

We are told that American business pays out $30 billion a year for health insurance benefits. This is an impressive figure indeed, but should it not also be pointed out that business lays out $100 billion each year to meet government regulations? Again I would ask, how much is too much?

Even though we may be able to rationalize the high cost of health care, it would be very unrealistic to go on about our business and hope the problem will go away. It will not. There is reason to believe the general public is becoming increasingly critical of medical costs. At a recent Hoffman-LaRoche marketing seminar the composite findings of six Lou Harris polls were reported. These are described in the January 7, 1980, issue of *Medical World News*. When asked if the government should put controls on doctors' fees, 51 percent of the respondents said yes; 37 percent no. The vote on hospital controls was 59 percent in favor and 28 percent opposed. On control of drug prices it was 66 percent for and 25 percent against. But the news was not all bad. The same polls reported that nearly 90 percent of those polled were pleased with the quality of their health care and 80 percent were satisfied with its availability. Stated briefly, these polls indicate

the public is satisfied with the product and its availability, but objects to the high cost.

Such an attitude on the part of the public should be of great concern to us. History has taught us that in a representative republic such as ours, politicians react *first* to public demand. Indeed, they must do so if they are to remain in public office. Therefore, the increasing demand for cost control—by whatever means—is quite predictable. No, the problem will not go away.

Cost Control Is Everyone's Business

When I hear my colleagues discuss cost containment (which is seldom), I hear the same attitudes being expressed over and over again. Most common is the attitude shared by bureaucrats: "I'm all for economy, as long as it doesn't affect my department." There is often a sense of hopeless resignation, or a comment such as "What can I do about it? My fees are certainly reasonable." I hope we are coming to realize that these attitudes simply will not do. If we are to continue our system of health care, cost control must become everyone's business—and now.

If cost control is to be "an inside job," just where then can health professionals look to trim costs? We must first realize that medical care decisions only affect about 10 percent of the areas impinging on total health care. It is unreasonable to expect the health care system to solve all the ills of contemporary America. If somehow we could convince American citizens to eat less, drink less, smoke less, exercise more, drive automobiles more carefully and get along better with their families, we could realize truly massive savings in terms of death and disability. It is not the purpose of this paper to engage in a philosophical discussion of contemporary lifestyles, or the means to convince Americans to adopt better health habits. It is to be hoped that this will happen and everyone will benefit. There is some small evidence that this is already happening. For example, deaths from stroke dropped 31 percent between the years 1972 and 1978. Heart disease mortality fell 18 percent between 1970 and 1977. It is our feeling that the development of better health habits and the treatment of hypertension were instrumental factors. Suffice it to say that any major breakthrough in conquering our major diseases will require a hard look at the so-called diseases of civilization. Instead, this paper will deal with economies that might be realized in our current health care system with the cooperation of the people and the agencies involved.

Dr. Max Parrott, recent President of the American Medical Association, has stated many times that in any health care system there are only three variables: cost, quality and access. If we attempt to change one we invariably influence the other two. First, let us consider *quality*. Everyone wants to maintain the quality of health care, perhaps even increase it, although Congress may be unintentionally impairing future quality by limiting research and teaching funds.

Limiting Access by Rationing

Probably the most important of the three factors is *access*. We have heard our political leaders and social planners make a big point out of a system that has *universal access*, although I do not think they quite mean it. This is often used as an argument for the development of Health Maintenance Organizations (HMO's) which is something of a paradox when we realize *their* success depends on limiting access. Certainly costs *can* be controlled by limiting access. The problem is to develop some equitable means of doing so.

Access has always been indirectly limited in the past by the factors of cost, geography, and the availability of facilities and personnel. What we are dealing with here is more direct limitation of access. This can be done and is being done in some countries of the world. For example, a government can rule that there should be no cardiovascular surgical operations, major joint replacements, or other costly medical and surgical procedures beyond a given age. Other devices are used, such as limiting the number of elective surgery beds and eliminating reconstructive and plastic surgical procedures, and by similar broad sweeping simplistic rules. Cost-effective—yes, but the quality suffers.

Some form of rationing will always be necessary. Our system of health care can and would expand indefinitely to gobble up every dollar made available to it. It would seem that in the very near future we are going to have to make some very difficult choices. Choices that involve just what we can do, for whom, when and where. One hopes that such choices will be based on some standard of *need* rather than on economics or social position. The development of such a

policy will involve many agonizing decisions and may very well involve persons and agencies outside the medical profession. We have already had some experience in this area. I would point to the regional dialysis committees, which functioned for years before Congress made end-stage renal disease a Medicare benefit.

If some reasonable rationing policy is not developed, for whatever reason, the federal government will certainly move in to fill the void. The inevitable bureaucratic superstructure will be formed, followed by a blizzard of regulations and restrictions. We have already witnessed a number of congressional proposals which, at best, would only chip away at the periphery of the problem of health care costs. Most publicized was President Carter's hospital cost containment bill, which would have placed a ceiling on hospital costs. This proposal was ill-conceived and patently unfair. Fortunately, Congress would not accept it in spite of enormous pressure by the Administration. Legislation continues to crop up dealing with HMO's—the government's favored health care delivery system which has hardly taken the country by storm. Most HMO legislation has been sold on the argument that it is cost-effective.

The Medicare and Medicaid amendments now before Congress also contain a number of cost containment features. Certificate of Need legislation is intended to restrict costs and "unnecessary duplication." A number of efforts are being made to extend these restrictions to doctors' offices.

I wonder if anyone considered the "certificate of need" principle during the recent bailout of the Chrysler Corporation? Could not the same argument have been used? Why should taxpayers bail out Chrysler Corporation when we already have two large automobile companies, not to mention the imports? Is this not unnecessary and expensive duplication?

There are a number of other congressional proposals, including several national health insurance schemes. Most of these involve prospective budgeting via capitation or negotiated national fee schedules (or both). Stated briefly, the federal government's solution to controlling costs is to place total dollar limitations on health care, then further control distribution of the funds by rules and regulations. If such a grand scheme comes to pass, *we* will be forced to make the painful decisions involved in the rationing of our health care services while trying to operate in a bureaucratic straitjacket. The spectre of more bureaucratic controls is enough to give us all nightmares—and not just bureaucratic controls in medicine, but those affecting all segments of our society. Mr. Griffin Bell, our recently departed Attorney General, likened the federal regulatory agencies to "an army of occupation," all powerful and universally hated.

Costs of Government Regulation

The staff of the American Medical Association recently assembled some figures on the cost and impact of these regulatory agencies. I will mention just a few. First of all, the cost to taxpayers for supporting these agencies ran $4.8 billion in fiscal 1979. Federally mandated safety and environmental features added $666 to the cost of an average automobile. Added up, this costs the American motorists about $10 billion per year. Private business invests more than 143 million man hours filling out federal forms, at a cost of $30 billion, even though the Federal Paperwork Commission conceded that "a substantial portion of this cost is unnecessary." Eventually all costs are paid by consumers. Economists have estimated that the total tab for government regulatory activities will approach $100 billion in fiscal 1979.

The available figures in the health care field are no less startling. In 1976 the Hospital Association of New York compiled statistics for 148 acute care hospitals and learned that 25 percent of hospital costs were the direct product of meeting government regulations—adding up to $1.1 billion annually. They also estimated that 56,000 full-time hospital employees are working on regulatory matters. Stated in a more practical way, $35.85 was added to each patient's bill each day to meet regulatory requirements. Certainly some regulation is necessary, but we have long since passed the point of diminishing returns. Simple logic would tell us that more money could be saved by streamlining the regulatory requirements than by adding more regulatory control, as would be required by a number of congressional proposals. The government needs to be reminded constantly that economy, like charity, should begin at home. Fortunately, we hope, the many complaints against overregulation have not fallen on deaf ears. In the current session of Congress more than 30 bills have been introduced on

the subject of regulatory reform. Most are targeted at the independent regulatory agencies, which in the opinion of many have overreached their authority. The greatest heat seems to be directed toward the Federal Trade Commission, but there are a number of others.

John Elliott, who contributes to the "Washington Week" column in *American Medical News,* made an interesting point in the December 28, 1979-January 4, 1980 issue. He suggested that at least part of the responsibility for the burden of overregulation should be borne by the health professionals. In his view we have failed to translate technological advances and new scientific knowledge into readily available facts. Surely a prime example would be computerized tomography. The $150,000 limit contained in Certificate of Need legislation was aimed at preventing the "unnecessary proliferation" of these expensive machines. Perhaps we should have taken more time to explain the economic savings involved. We should have explained that many complex and expensive neurological procedures are now virtually obsolete, and to the patients' gain. I am sure there are many more such examples. In other words, we need to lend some of our expertise to the regulating agencies to help separate the necessary from the oppressive, to develop lean efficient management rather than burdensome bureaucratic overlap. Certainly this idea is worth pursuing.

The thought occurs to me that the Joint Commission might consider taking over the responsibility of helping us unravel the regulatory mess. I am aware that many of my colleagues will object to the Joint Commission assuming any greater authority than it already has, but at least the doctors in this country have a good deal more input in its decisions than we have in most bureaucratic agencies. There can be little doubt that a rational approach to the regulation and inspection of hospitals and health facilities could result in very worthwhile economy.

Voluntary Effort in Cost Control

If cost control is to be the major thrust of this decade, where else can we look for economies without sacrificing quality or impeding progress? Apparently there are some areas. I would point to the success of the Voluntary Effort program. It appears that this jointly sponsored program has succeeded in blunting the spiraling cost of hospital care. Hospital utilization is a favorite scapegoat for our social critics—often the same ones who want to guarantee universal access. In fairness, we must admit that a firm but fair hospital utilization policy will save money, but not where most people think. A long-term hospital admission is nearly always justified. The studies of Dr. Virgil Slee have proved this. Very rarely are people admitted to hospitals who do not belong there. The real economy in hospital utilization is eliminating those "questionable days" on all patients. This has been successfully accomplished in several areas of the country.

The overutilization of expensive hospital technology is a commonly heard criticism. Computerized tomography is usually singled out, along with nuclear imaging, ultrasound scanning and the like. Yet the Robert Wood Johnson Foundation concluded from their study that reducing the annual operating costs of the nation's four most complex technologies by half would produce a net savings of less than 1 percent of the 1978 health care expenditures. Rather, it is the collective expense of minor medical tests and procedures that have the greatest impact on the total medical bill. If every practicing physician would reduce his use of these minor tests and procedures to the bare minimum consistent with quality care, the savings would be substantial. This is especially true in teaching institutions.

I have a suggestion to make here that might help us all become more cost conscious: putting the *price* of every laboratory test, x-ray study, electrocardiogram, and the like, on both the requisition and the report in a prominent enough place that the attending physician will be sure to see it. I am convinced that it would have a measurable effect on all of our hospital order-writing habits. I am also sure that we would soon be making greater use of outpatient and day care facilities and preadmission workups, all of which should reduce the total cost.

Impact of Health Insurance Benefits

There is another major influence in health care utilization that deserves some rethinking and that is health insurance benefits, from whatever source. For at least four decades the major thrust of industry, labor and the health professions has been for bigger and better health insurance contracts. It is well known in the insurance industry that the more benefits are offered the more they will be used. Besides, it is only human nature for a person to use a benefit that costs him little or

nothing. As a result, our total health insurance costs are reaching astronomical levels, with no end in sight.

To be sure, the elimination of first dollar coverage, deductibles and coinsurance can help reduce this cost, but often in the wrong places. The impact is greatest on the low economic levels. The administration of the program is complex and the system can be manipulated by the unscrupulous. The National Commission on the Cost of Medical Care recommended the "consumers' choice" principle among health insurance plans. The idea is for the consumer to shop around and buy the plan that is the best deal for him. Several members of Congress have seized on this idea and carried it one step further. Senators Schweiker and Durenberger and Representative Ullman have developed programs that limit to a fixed amount the contribution an employer can make to his employees' health insurance program, that amount pegged at the average cost of federally qualified HMO's throughout the country. In addition, the employers would be required to offer at least three health insurance plans. If an employee wished to have greater coverage than offered, the cost of such coverage would be his own responsibility. Under at least one plan, if he carries a less expensive program, the difference in this "fringe benefit" would be refunded to him as additional income. Obviously the federal government looks on these plans not only as a means to control spiraling health insurance costs, but to recover substantial amounts of "lost" tax revenue. It should be added that although these three plans vary in detail, the idea of a maximum allowable contribution by the employer is common to all of them.

If one of these plans were to become law, I can foresee many howls of anguish on the part of the public and many problems for those of us in the health professions. However, such a plan would succeed in shifting part of the cost of health insurance back to the individual person, which in turn would surely have its impact on health care utilization. Thus, some economy would be realized. Whether or not this has great influence on health care and on individual health is another problem.

I think it should be pointed out here that Congress is not so much interested in the actual cost of the health insurance program to the individual consumer as it is in the spiraling cost of the Medicare-Medicaid program. Trying to get a handle on these costs has been responsible for much of the proposed legislation affecting the health care industry. It prompted the President's hospital cost control bill. It has sponsored any number of proposals that attempt to expand the HMO system in this country. There are a number of Medicare and Medicaid amendments designed to encourage doctors taking assignment under Medicare, and even the national health insurance programs have cost control as one of their initiating factors. There are a number of congressmen and powerful lobbyists who feel that the increasing costs of the federal health programs can be controlled only by completely revising the system. All of which brings us back to our original point: cost control should be the urgent business of all health professionals.

Private Sector Initiatives

Some progress has already been made by the private sector. The Voluntary Effort of hospital cost containment has certainly been successful thus far. Increases in doctors' fees nationwide are now lagging behind the Consumer Price Index. Walter McNerney, President of Blue Cross and Blue Shield Associations, recently reported a sharp drop in hospital utilization, while at the same time hospital outpatient visits rose dramatically. Evidently there are some areas where hospital costs and utilization can be reduced.

Organized medicine could and would be more active in controlling excessive fees were it not for recent Federal Trade Commission (FTC) rulings in this area. Evidently the FTC is of the opinion that reviewing doctors' fees suggests price fixing. Here again, the medical profession has been placed in a *no win* position by the rulings of federal agencies. We have, on the one hand, been criticized sharply by government leaders and others for "not policing our own." When we attempt to do so by monitoring our own fees we are threatened with antitrust litigation. This paradox ought to infuriate everyone. Apparently the federal government is free to fix prices by recommending national or local fee schedules, but when organized medicine attempts to protect the public from fee-gouging we are in violation of federal statutes—at least as interpreted by the Federal Trade Commission.

Right here is another great inequity in our system of government. The mere *threat* of legal

action by the Federal Trade Commission or other regulatory agency is enough to intimidate all but the hardiest (or perhaps fool-hardiest). It is scarcely a fair fight. The agency has almost unlimited resources at its disposal, in contrast to the private organization which must make a substantial financial commitment to provide the necessary legal costs. Even winning such a battle constitutes a Pyrrhic victory.

The American Medical Association, among others, is attempting to correct this inequity with a federal statute. Under the provisions of this bill administrative agencies would be required to reimburse victorious *defendants* in actions initiated by the agency for reasonable attorney fees and other costs directly related to the defense of the action. Such a law would make it a great deal easier to fight unfair government regulations. One hopes that it would also encourage agencies to give pause before issuing unwarranted regulations.

All of the items I have mentioned can have their impact on cost containment and all need to be vigorously pursued. But, in my view, the single greatest economy would result from a critical review of the entire regulatory process. We need to streamline the necessary and eliminate the unnecessary. A rational policy of regulations will require the expertise of health professionals. I am sure that expert advice and counsel would readily be offered if the opportunity was given. Somehow we must shed this crushing burden from the health care system. The need is urgent.

In the Trenches, Cost Containment Ain't Always Easy

An Illustrative Case Report

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A specific case report illustrates the interplay between human considerations and technological potency that makes cost containment difficult in the real world of medical practice.

WE HAVE GREAT TECHNOLOGICAL ABILITY available to us in diagnosis, perhaps even more than in treatment. Unfortunately, it is often very expensive. When we are unraveling a problem, deciding on a possible course of action and considering the value of that action, we depend greatly on these expensive modalities and tend to forget the ultimate financial cost to the patient and to the *system*. A case in point follows.

Report of a Case

An 83-year-old woman was eating her lunch when she suddenly stiffened, her legs shot out and she was, in effect, ejected from her chair. She landed face down on the floor striking the right side of her face. She was then totally unresponsive and an ambulance was called.

She was beginning to respond and able to follow simple verbal instructions when she was first evaluated by an emergency room physician 45 minutes after the initial episode. She had a 4-cm hematoma of the right parietal region of her scalp, a minor laceration of the bridge of her nose and a more extensive laceration of her lower lip. A neurological examination showed flat optic discs (seen around cataracts), generalized hyperreflexia and bilateral up-going toes on plantar stimulation. On cardiovascular examination she had a grade 4/6 systolic murmur along the left sternal border radiating up the left side of her neck. There was a faint diastolic murmur present as well. There was no sign of congestive failure.

An electrocardiogram showed frequent ventricular ectopic beats, occasionally multifocal and occasionally in ventricular bigeminy. She was given two intravenous "pushes" of lidocaine, 50 mg each. A lidocaine infusion at 2 mg per minute was started. On portable x-ray studies of the chest and skull there were no significant pathologic findings.

The patient's usual internist was on vacation. Therefore his alternate was called and saw the patient approximately an hour after her arrival in the emergency room, as the above evaluation was being completed. His examination confirmed the original findings. By this time she was responsive and able to converse. She had no memory of the immediately preceding events. Because of the loss of consciousness and the cardiac arrthythmia, admission to the medical intensive care unit was arranged.

Her family was able to provide a pertinent past history. About 18 years before this admission, the patient had had an acute myocardial infarction with good recovery. Fifteen years before, her peripheral circulation was investigated because of claudication. Pronounced atherosclerosis from the renal arteries distally was found, with almost complete obstruction of the femoral arteries.

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Significant calcific aortic stenosis was noted at that time. Following another acute myocardial infarction eight years before this admission she had an episode of acute congestive failure and a deep thrombophlebitis developed in her left leg. Ten months before this present admission, she had a cerebral arterial occlusion that left her with a mild left-sided weakness and a moderately severe impairment of language skills because of a short attention span, memory defects and inability to select words. She was capable of feeding and dressing herself but required supervision for most elements of daily living. Medication each day consisted of 0.125 mg of digoxin, one triamterine-with-hydrochlorothiazide capsule and one probenecid-with-colchicine tablet.

On admission to the coronary care-medical intensive care unit, another electrocardiogram and another portable x-ray study of the chest were done because of standing orders. The monitoring electrocardiograph continued to show the frequent multifocal ventricular beats. The lidocaine drip was continued. Her condition remained static except for some diminution of the frequency of the ventricular ectopic beats during the second hospital day. According to standing coronary care orders additional electrocardiograms were made on three successive days. Myocardial isoenzyme determinations were repeated three times and showed no significant increase. The SMA 12/60 panel done on admission was repeated at 12 and 24 hours. Electrolyte values were normal. The blood urea nitrogen level was elevated at 37 mg per dl. The creatinine value was 2.0 mg per dl and the uric acid level was moderately elevated.

On the day after admission, the lidocaine infusion was reduced to 1 mg per minute. An electroencephalogram showed evidence of diffuse and focal organic brain disease. Administration of dilantin was started in an oral loading dose of 300 mg every two hours for three doses and continued at 300 mg per day. The patient remained alert and responsive with the same degree of amnesia that antedated admission.

Toward the end of the second hospital day in spite of the continued lidocaine drip, spells of ventricular bigeminy occurred. Quinidine sulfate therapy was started in oral dosage of 300 mg every six hours. About 40 hours after admission the patient had persistent runs of ventricular bigeminy and was given two "pushes" of 50 mg of lidocaine about two hours apart. Through all of this the patient remained asymptomatic. One hour later there was a short run of ventricular tachycardia and another two 50-mg boluses of lidocaine were given intravenously. The infusion was increased to 3 mg per minute. Lidocaine and digoxin levels were determined to be in the therapeutic range. Three hours later the ectopic beats were largely suppressed and the lidocaine was reduced to 2 mg per minute.

At this time she was seen in consultation by a cardiologist. Shortly after this she again lost consciousness. She was not observed to convulse and returned to full consciousness slowly over two hours. The lidocaine administration was temporarily discontinued, then resumed after three hours at a rate of 2 mg per minute. She was given a larger "loading dose" of quinidine. The digoxin and furosemide therapy was continued in daily doses.

It was thought advisable to evaluate the degree of aortic stenosis to guide further therapy; therefore an echocardiogram, phonocardiogram, exercise tolerance cardiogram and apex cardiogram were ordered. These tests were ordered on Sunday, and consequently there was a one-day delay before they were done. These indicated a significant, perhaps severe, degree of aortic stenosis. Cinecardiography showed a heavily calcified aortic valve and prominent calcification of all three coronary arteries.

Before more extensive studies (such as cardiac catheterization and coronary angiography for which facilities were easily available) a neurological consultation was obtained. Oculoplethysmography and cerebral Doppler studies did not show significant occlusion of the carotids. History and physical examination determined that her preexisting level of disability did not justify heroic corrective procedures in the cardiovascular system. A computerized tomographic brain scan was not done.

She was transferred out of the intensive care area to a semiprivate room. Physical therapy was ordered for gait retraining and to restore muscle strength. She complained of considerable low back pain so x-ray studies of the lumbar spine were ordered to be sure she had not had a compression fracture as a result of her fall. The nursing staff reported significant rectal bleeding and a sigmoidoscopy was scheduled. After sober reflection, this was cancelled. The patient was discharged home requiring a full-time attendant, ambulatory

with assistance. Her medications were as on entry plus quinidine and phenytoin.

Discussion

In this case, there was some thought given to cost control and to using available noninvasive procedures. However, costs mounted.

The patient spent five days in the coronary care-medical intensive care unit area with constant electrocardiographic monitoring at a cost of $2,475. (The next five days were in a semiprivate room for $1,150.) Four electrocardiograms were done in addition to the monitoring, cost $209. Four x-ray films of the chest, cinecardiography, a skull series and x-ray films of the lumbar spine came to $606.50.

Serum electrolytes were measured five times ($195). The 12-test chemistry panel was done twice and a complete blood count four times. Arterial blood gases were determined twice for $213, which included the arterial punctures. Three digoxin levels cost $175.50, two quinidine levels were $82.50. The total clinical laboratory charge was $1,227.50.

Echocardiography, phonocardiography and a modified exercise tolerance test totaled $440. Oxygen therapy amounted to $214. With emergency room charges, pharmacy, central supply and physical therapy, the total hospital bill reached $6,988.

Physician charges totaled $895. This included a plastic surgeon for the repair of the lip, two cardiologists, one neurologist and the primary physician (who visited the patient several times a day for the first five days).

In retrospect it would be possible to indicate that certain procedures could have been omitted. However, in reviewing the record, including the extensive nursing notes in coronary care and the progress and consultation notes, it is evident that procedures were indicated at the time they were ordered for very specific reasons. The physicians felt at the moment that these tests and procedures were indeed necessary for proper evaluation and treatment. Some effort was made to avoid using the more expensive modalities at our disposal but the total cost of care for the ten-day episode was $7,883. That is impressive.

Cost Containment: An Economist's View

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Rising medical care costs are not the problem they seem to be, in part because quality of care is not considered. The problem may be more the absence of choice of alternative health benefit packages with price differences. The future of health services in the United States will have more competing alternatives requiring physicians to be more cost conscious.

NOW I AM NOT a card-carrying, board-certified and fully licensed medical economist. In spite of this and other shortcomings too numerous to mention, let me answer a few basic health economics questions in a way that cuts through the arcane words and numbers with which economists usually surround themselves.

Q. Is there a medical care cost crisis?

A. No.

The cost "crisis" is largely a figment of regulators, administrators, bureaucrats, reformers and academics wishing to justify their existence and preach reform. If there were a crisis, costs could be cut by draconian methods. Last year the University Hospital of Sao Paulo, Brazil, requested a budget from the government of $200 million and received half of that. The result was unused and unstaffed beds, long waiting lines and cost control (Dr. Humberto Novaes, Sao Paulo, Brazil, personal communication). In the United States, if Medicare paid 50 cents on the dollar, this too would answer the cost problem. There may not be a crisis, but there is always, in any business or profession, a problem of cost control.

Q. Are rising medical care costs a new problem?

A. No, but the rate of growth is.

Consider the costs per patient discharged alive from a major teaching hospital from 1823 to 1970 using 1967 dollars which adjust for inflation in the rest of the economy[1] (see Figure 1).

In this way differences in number of patients admitted and length of stay are accounted for by using costs per patient discharged. Excluding deaths from the denominator very roughly adjusts for quality of care provided. Research and teaching have always been goals of this hospital and these costs are included throughout. In 1823 the adjusted cost per live discharge was $112. A century later this cost had doubled to $217. During the next 25 years, 1923 through 1948, it doubled again to $410. In the next 17 years it doubled again; $849. In the next five years, 1965 through 1970, it almost doubled again—$1,439. Extrapolating from this exponential growth curve shows that these adjusted costs per case should have reached infinity by the start of 1975. However, sensible behavior on the part of government, administration, doctors and patients, but not necessarily in that order, kept the rate of rising hospital costs somewhat below that. Viewed this

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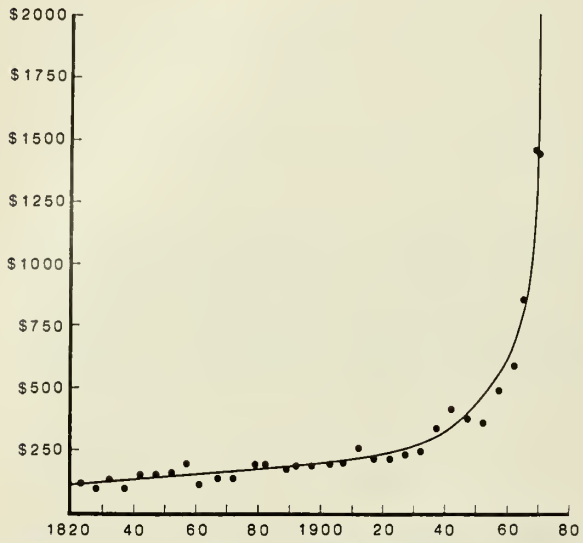

Figure 1.—Cost per patient discharged alive in a major teaching hospital, 1823 to 1970, using 1967 inflation-adjusted dollars.

way, the hospital fought and won the battle to control costs in the beginning of the last decade. Now costs are rising for medical care as a whole at a rate closer to 16 percent.

Q. Is there inflation in medical care?

A. Probably not.

Inflation means the same thing costs more today than it did before. A gallon of gasoline is the same today as ten years ago, but now it costs more and that is inflation. Consider a haircut which costs a lot more today than it did in 1925, but it is not the same haircut. Find an old-fashioned barbershop with oak paneling, marble sinks, your own shaving mug, and think of that lost era of hot towels, thick lather and fine service. Today you can pay $6 for what may have cost 25 cents then and was better. That is inflation. However, if your thing is the latest unisex hair style, created with blow dryers, hair tinting and the wonders of modern tonsorial science, then you may be happy to pay $15 for this rather than 25 cents for a 1925 haircut. If so, there is no inflation for you. (These ideas came from the late Professor Reuben Kessel, personal communication.)

Would you rather pay $112 for having your case of syphilis treated by four weeks in the hospital of 1823 with large daily doses of mercury, or would you prefer today's treatment at today's price? If you choose the latter, there is no inflation because quality has outpaced price. Would you prefer to have your hernia operation in 1935 for $410 when there was a 5 percent operative mortality, or would you rather pay about $1,500 (or less) today when the operative mortality is way below one percent?*

There are probably other medical problems in recent years where costs have gone up and service rates have not changed.[2] If you are interested, pull charts of similar patients today and ten years ago. Ask yourself this question: If I have to pay all the costs out of my own pocket, would I like to have yesterday's care at yesterday's prices or today's care for today's prices? Your answer will define whether inflation exists or not. Truly measured inflation is subjective and personal because it includes both costs and quality which are in part in the eye of the beholder.

Q. Is the federal government worried about medical care inflation?

A. No, they do not measure it. They only measure cost changes and not quality changes.

Q. Is the federal government worried about medical care costs?

A. Not very much.

After all, the Carter "cap" proposal to limit hospital costs did not win congressional approval. That the voice of the special interests involved swamped the public and administrative voice is another way of saying the same thing.

The real reason the government is not very concerned is the graduated income tax. Inflation in the economy as a whole is a good thing for the federal government. Consider the physician with a taxable income in 1977 of $67,000. He paid 36 percent of this or $24,120 in federal income taxes. Now assume his taxable income was increased by 10 percent in 1978. He is taxed on this added $6,700 income at the rate of 55 percent or $3,685. (This analysis comes directly from the 1978 Federal Income Tax Forms, Department of the Treasury, Internal Revenue Service.) Thus, this doctor's after tax income increased by 4½ percent, while the federal government's income rose by greater than 15 percent. Given a 10 percent rate of inflation, the government is better off and the doctor is worse off. This way

*Ms. Karen Schachter, Jerusalem, Israel, provided help in collecting historical data, and the Cleveland Foundation through the Health Systems Management Center, Case Western Reserve University, assisted with support.

the government can pay for rising total Medicare and Medicaid costs without raising the tax rate or cutting other services.

Q. Why are medical care costs rising so fast in the last few decades?

A. Because doctors are doing what society wanted them to do, and hospitals are mostly nonprofit organizations, and because of health insurance.

As Blanpain[3] points out in a historical survey of European medical care, health insurance was put in place to assure access by all first to doctors and then to hospitals. Only much later did the need for cost control arise. Health insurance exists to make it possible for everyone to get the best medical care without regard to cost. Doctors responded by providing care and demanding the best hospitals and most modern equipment for their patients. Coupled with unprecedented funding of medical research, an avalanche of new medical procedures, drugs and equipment were introduced and rapidly adopted, amid loud public applause. National health insurance programs called for this response. Only much later did society and government realize that all this care was expensive. When Medicare and Medicaid were passed in 1966, it was assumed that being a patient takes time and is generally unpleasant, so people would not use too much care. It was assumed that medicine was a clear-cut science where an illness is precisely defined and equated exactly to a specific appropriate treatment. These treatments multiplied by a clearly defined need would define total medical costs.

By contrast, imagine what would happen if there were national movie insurance so that all, regardless of ability to pay, could improve their quality of life by seeing all the movies they needed—where "needed" is defined by movie experts, or if you really wish to be cynical by professors whose research grants are paid for by movie companies.

If the movie studios were run for a profit under these circumstances, there would be no profit too large for the stock owners. If the movie studios were nonprofit organizations like hospitals, there would be no salary too high for the executives and their paraprofessionals; and from the studio's perspective, the cost of producing a movie could never be too large.

In Europe and the United States, hospitals are largely nonprofit (government or private) and the locus of much expensive medical care. Money raised through third parties does not go into profits, but into more staff, more tests, more research, more services and more beds; thus, increasing costs and possibly improving quality (personal communication from Professor Ralph Benny). Large teaching hospitals lead the way and set the standards which become accepted medical practice and spread throughout the world.

Since doctors order the tests, prescribe the drugs and admit the patients, they are blamed for all this increase in services and costs.

Q. You mean that doctors have been following the wishes of society to provide the best care regardless of cost, and now instead of being praised for their social responsibility they are blamed for the consequences?

A. Yes, of course.

Now doctors are hearing the new social signals about cost control, and in my opinion, they are once again being socially responsive. It is hard nowadays to find a physician who is not well aware of medical costs and is not thinking hard about cost control. Doctors are aware that insurance payments are sending out screwy signals. Third parties reward doctors for doing and not for thinking, and they reward some specialties more than others for no rational reason. However, economists would say that doctors' cost concern will only be transformed into actual practice when the economic signals point that way.

Q. What answers do health economists offer?

A. More competition.

Perfect competition, like the perfectly healthy person, never occurs but is a useful fiction. Health economists spend a lot of time thinking about how the medical care market departs from pure competition. (Table 1 gives a basic readable bibliography in medical economics.) Competition requires lots of buyers and sellers choosing and pricing without restriction. The economist Milton Friedman, always one with a startling idea and never one to worry about political practicality, proposes the complete elimination of licensure so anyone can become a doctor.[4] Martin Feldstein proposed that there be very large health insurance deductibles so patients must pay for most of their

TABLE 1.—*A Basic Readable Bibliography In Medical Economics*

Bunker J, Barnes BA, Mosteller F (Eds): Costs, Risks and Benefits of Surgery. New York, Oxford University Press, 1977
(What are the costs and benefits of some frequently done surgical procedures?)

Carels E, Neuhauser D, Stason W: The Physician and Cost Control. Cambridge, MA, Oelgeschlager, Gunn & Hain, 1980
(What physicians can do about medical care costs.)

Culyer AJ, Wiseman J, Walker A: An Annotated Bibliography of Health Economics. New York, St. Martins Press, 1977
(1,500 papers collected by three English economists.)

Enthoven AL: Consumer-choice health plan. N Engl J Med 298:650-658, 709-720, Mar 23, Mar 30, 1978

Feldstein M: The Rising Costs of Medical Care. Washington, DC, Information Resources Press, 1971
(The standard economic explanation.)

Feldstein P: Health Care Economics. New York, John Wiley & Sons, Inc., 1979
(A basic textbook.)

Friedman M: Capitalism and Freedom. Chicago, University of Chicago Press, 1962
(Chapter 9 on medical licensure.)

Fuchs V: Who Shall Live. New York, Basic Books, 1974
(Health, economics and social choice, a good place to start.)

medical care themselves.[5] He assumes that if a patient has to pay himself, he will be more careful in his choices. Alain Enthoven proposes that there should be competing alternative delivery systems such as Health Maintenance Organizations (HMO's) and fee-for-service insurance, which each worker can choose from through his place of employment.[6]

The genius of Enthoven's proposal is not that it is new, but rather that it defines what is actually occurring and therefore politically has the greatest likelihood of coming into being as the basis for the future of medical care in America.

The idea that patients may wish to choose between different ways of paying for their medical care has a long history. The oldest statement about American medical economics known to me was by Dr. William Douglas of Boston in 1721.[7] He offered his patients the option of fee-for-service payment or "five pounds per annum sick or well." Thus, to use today's jargon, Dr. Douglas offered his own IPA-HMO (independent practice association-HMO) option.

Transforming Douglas's solution to today's world would suggest five basic choices with associated price differences reflecting different deductibles in workers' paychecks. These are as follows: (1) The usual fee-for-service health insurance coverage with minimal deductibles and high and low cost options that might include or exclude such benefits as extensive ambulatory psychiatric coverage. (2) Major medical insurance at low cost but with a very large self-pay deductible; say $2,000 per family per year. (3) Prepaid group practice HMO, like Kaiser-Permanente. (4) An IPA-HMO where the private practice primary care doctor offers patients care for a fixed yearly amount, as Dr. Douglas did. (5) Other arrangements for special groups such as the Indian Health Service and Veterans Administration care for disabled veterans.

Although there will be different levels of payroll deductions, probably most people will choose the high cost, full coverage options implying that people will still pay for more medical care.

The role of government will be to assure that everyone has good basic coverage, but not necessarily pay for the highest cost option. Because people and the government do not have price options, they cannot easily choose a lower cost option. Thus, the problem of medical care costs is really more one of choice than of cost.

Q. So if there is no problem with medical care costs, doctors do not have to worry about it any more?

A. No, just the opposite. Competing alternatives will mean doctors have to worry a whole lot more about costs than they have in the past.

Q. What should physicians do about costs?

A. Several things.

Like William Douglas, primary care physicians should offer their patients a capitation option. For patients who plan to pay for much of their own care, be prepared to advise them on the availability of lower cost options, such as outpatient surgical procedures, and the impact of behavior change such as weight reduction on their future medical care costs. Make sure that employers offer price differences associated with the different medical care options they present, so that

when people choose the high cost option, doctors can point out that people want to pay more for medical care. To a large degree this will take medicine off the hook. Doctors should make more effort to demonstrate the reality and the magnitude of the benefits provided by medical care. Too many medical procedures have not been carefully evaluated and rarely are there good descriptions of the magnitude of the expected benefits of care.[8] Just what is the size of the benefit for surgical treatment of silent gallstones, of hernia operations in the elderly, of fetal monitoring? There is a lot to be done.

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The Primary Care Network

A New Type of HMO for Private Practice Physicians

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A new type of health maintenance organization has been developed to encourage primary care physicians in private practice to become coordinators and financial managers for all medical care. Each patient chooses one internist, family or general physician, or pediatrician and must be referred by that physician for all hospital admissions and care by specialists. The primary care physician authorizes all payments from his own account for care provided to his patients. He shares any deficit or surplus remaining at the end of the year.

Hospital admission rates and length of stay are lower than those of Blue Cross, with only one of three dollars paid to hospitals. The plan is providing care to 38,000 persons with 750 participating physicians in Northern California, Washington and Utah.

This plan represents an attempt by physicians to control costs without government regulation.

THE MOST SERIOUS THREAT to our present way of practicing medicine is spiraling costs. As costs of medical care continue to escalate there is more searching for rational and practical ways to halt the cost spiral. One of the major problems is that all the involved parties are insulated from the cost implications of their individual decisions. Employees and unions are pressing for first dollar coverage for all medical and dental care because those benefits are not taxed whereas salary increases are. Insurance companies are protected by their ability to pass along increased premiums in a noncompetitive environment. Physicians are insulated by the third party payment mechanism.

With third party payment there is less reason for a physician to use restraint in ordering more tests. A thorough and expensive diagnostic workup for a simple complaint will not cost the doctor anything and might benefit the patient. The fact is that most expenditures will be paid on a "no questions asked" basis by some large and impersonal insurance company which will be able to spread the expenditure over a large number of enrollees and raise premiums the following year. This relieves the physician of any need to consider seriously the cost-benefit aspects of his decisions. The current fee-for-service, third party reimbursement system is behaving exactly as it was structured to behave. Costs will continue to escalate so long as patients, physicians and insurance companies are insulated from the cost implications of their individual decisions.

Physicians, because of their key role as decision makers in the medical delivery system, determine either directly or indirectly most health care expenditures. The insurance companies, foundations and health maintenance organizations (HMO's) have no way to control expenditures except through physicians. The challenge

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for a practicing physician is to use his pivotal position to effect some control of escalating medical costs within the private sector, and thereby avoid further government regulation to control the escalating costs.

Since we as physicians find ourselves, willingly or not, in the position of gatekeepers to the rest of the medical delivery system, we must accept the responsibility to control costs or default to the state and federal governments who paid 41 percent ($78 billion) of all health care costs in 1978[1] and therefore have a compelling reason for halting the cost spiral. The necessary increase in defense spending and the push for a limit on government taxation make the case for government action to halt spending on medical care even more urgent.

Cost Control Through Competition

In the last two years there has been a reawakening of interest in structuring a medical marketplace that would promote cost control by competition between groups of providers. If competition within the private sector is to remain a viable public policy option to more government regulation and government control of the medical delivery system, then there must be expansion of alternative delivery systems which aim to impede escalating medical costs by organizing the delivery system more efficiently. These efficient alternative delivery systems can take many forms. Closed-panel HMO's such as Kaiser-Permanente and Group Health Cooperative of Puget Sound have proved their ability to substantially reduce hospital admission rates and health care costs. Foundations and other types of independent practice associations have in some cases altered practice patterns of their participating physicians by imposing strong utilization reviews in order to lower medical case costs.[2] This occurs especially in areas such as Minneapolis where there is strong competition from other HMO's.[3] An alternative to imposing controls on a physician's use of hospitals to contain costs is restructuring the incentive in such a way that the physician is vested in the savings which result from his efforts to control costs and maximize efficiency in the delivery system.

Incentive Reimbursement System Design

One type of incentive reimbursement system is exemplified by United Healthcare (UHC), a capitated primary care network type of independent practice association. This is a private sector, office-based, incentive reimbursement plan which restructures the incentives in order to encourage physicians to control costs and maximize efficiency. This model was initially launched five years ago in Northern California and Washington state by SAFECO Insurance Company with headquarters in Seattle. It was initially called Northwest Healthcare in Washington state and the SAFECO Health Foundation in California. It has recently expanded to Utah and has taken on the new name of United Healthcare in all three states.

There are three important features of the UHC system. First, it is a primary care physician network. The entire health care delivery system is organized around primary care physicians (internists, general physicians, family physicians or pediatricians). The plan contracts with primary care physicians who are in private practice in the community. They become the *general managers* or *gatekeepers* for specialty referral, emergency room use and hospital admission. If a patient wants to go to a specialist or an emergency room for nonemergent care, without the approval of the primary care physician, he must risk paying for it. At enrollment, each patient selects a physician from a list of those participating (usually 60 percent of the primary care physicians in an area participate before the health care plan is offered to employed groups). The patient then obtains all care from that physician or, on his referral, from others. That physician controls specialty referrals, hospital admissions, diagnostic tests and prescriptions by his power to deny payment for these services if they are undertaken without his authorization. When authorized by him, all medical care is paid, with virtually no deductibles or co-payments except for a $2 charge for each prescription.

The second important feature of this plan is that each primary care physician becomes the financial manager for costs of care to his patients. Premium dollars are paid to the plan in monthly installments by employers or patients. At present about 14 percent of the premium dollars represent administrative, marketing, and reinsurance costs and profits. The balance of the premiums is placed into the accounts of the 750 participating physicians. The amount placed in each account to cover total costs of care is calculated on the basis of age and sex of the physician's patients. Actuarial estimates of average community costs for total care in that geographic area are used

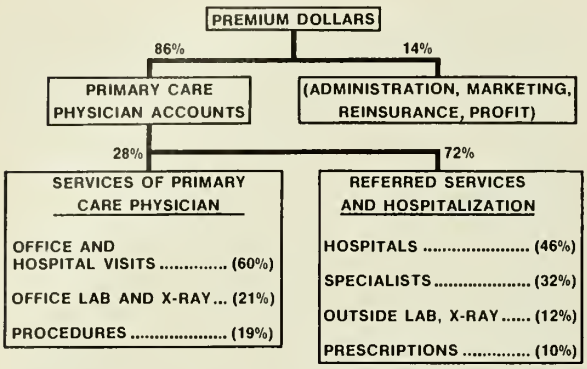

Figure 1.—Cash flow in United Healthcare, 1978.

initially and then modified according to actual claims experience for different age groups.

Figure 1 shows how the premium dollars are disbursed. The first part of the account covers the primary care physician's services. If the physician has fewer than 200 patients, he is reimbursed for his office and hospital visits on a fee-for-service basis. He receives 95 percent of his normal charge for the service. If the physician has more than 200 patients, he is paid a fixed monthly amount determined by the age and sex of his patients and the services he provides. A monthly check is sent to the physician, creating a regular and dependable income that carries minimal risk for underpayment once the number of patients exceeds 200.

The second part of the account receives about two thirds of the premium dollars and is used to pay for services other than those provided by the primary care physician. For example, hospital care costs, referral care, procedures carried out by other physicians, emergency room treatment, laboratory work and x-ray examinations done elsewhere, and prescriptions are all paid from this second part of the account. The plan reimburses specialists and hospitals on a fee-for-service basis only after the primary care physician has reviewed and authorized payment—to keep hospitals and specialists from overcharging as well as to promote cost consciousness in making future referrals. A monthly financial statement summarizes how the dollars for referral and hospital care have been spent. Both the mandatory review process and the monthly statement serve to educate the primary care physician about the costs of hospital and specialty care and encourage cost-effective referrals.

In addition to the education about costs of hospital and specialist care, there are incentives to encourage the primary care physician to give serious consideration to his new role as the coordinator and financial manager of all medical care. At the end of the year, any deficit or surplus in his own account is shared by the physician. If there is a deficit, the physician is required to pay up to a maximum of 10 percent of his own fee-for-service payments back to the plan. If there is a surplus, he keeps half of it; the other half is retained by the plan. Catastrophic costs (more than $5,000 per year per patient) are removed from any risk-sharing arrangement.

The purpose of these incentives is to give each primary care physician a vested interest in the costs of referral and hospital care, so that he will help coordinate health care delivery in the most cost-effective way. Because each primary care physician has his own account, a physician's efficiency is not diluted by other inefficient physicians, even among partners in a group practice. It is this individual account with built-in incentives for efficient coordination of the whole delivery system that is unique in the UHC system. The individual physician has incentives to refer his patients to specialists who perform outpatient surgical procedures instead of admitting his patients to hospitals, to ask specialists or hospitals why diagnostic tests or routine preadmission screening has been repeated, to find efficient laboratories, to prescribe generic drugs, to see patients in the office rather than in hospital emergency rooms, and to spend time on prevention and health education. In essence, then, the individual primary care physician becomes a one-man HMO.

While the traditional, uncontrolled fee-for-service system gives physicians an incentive to provide both unnecessary and necessary care, this new primary care network provides an incentive to underprovide necessary care. To deal with this problem, the plan reviews utilization to detect patterns of under-service or under-referral. Quality of care is also reviewed on the basis of criteria developed for ambulatory care. Quality assurance of hospital care at present is left to individual hospitals. When substandard patterns are found, attempts are made to educate the physician to change the patterns. The actions of recalcitrant physicians are discussed before the advisory board, which is composed of three participating physicians. No physicians have been terminated from the plan, but six have been put on probation. The most important precaution against under-service or under-referral is a patient's op-

tion of changing to any other primary care physician participating in the plan or of switching to an alternative insurance plan.

This leads us to the third important feature that differentiates this plan from other types of HMO's. By offering a wide selection of primary care physicians, it preserves existing physician-patient relations, styles of practice and facilities while introducing coordination and management by primary care physicians. Since United Healthcare is usually offered to an employer after 60 percent of the primary care physicians in the area are participating in the plan, most patients can continue to receive care from their physicians when they join the plan. They also have a much wider selection of referral specialists and hospitals (subject only to their primary care physician's approval) than in a closed panel HMO.

United Healthcare Results

Perhaps because of its ability to expand into new areas without large start-up costs United Healthcare has doubled its total enrollment each year for the past five years. The plan now provides care to 38,000 persons and has 750 participating physicians. Half of these physicians are family or general practitioners and the other half are internists and pediatricians. All are in private practice, with the exception of two family medicine residency programs and one group of university physicians. About 60 percent are in solo practice and the remainder in partnerships or groups. Three fourths of the participating physicians still have fewer than 50 patients enrolled. Thus, 95 percent of their income is still derived from patients who are not participating in the UHC system. Fifty-two percent of the physicians had surpluses in their accounts at the end of 1979. The average share of the surplus paid to those physicians was $413; the highest amount paid was $5,007. For the physicians who had deficits, the average share paid back was $169; the largest amount paid back was $1,833.

A recent survey of the physicians participating in United Healthcare has shown nine out of ten to be either satisfied or very satisfied with the plan. Those features which the physicians liked most about the plan included the ability to coordinate total patient care, the prepaid coverage afforded the patient and the belief that the plan does control health care costs. The feature that the physicians liked least was being personally at risk for the total health care cost.

The UHC plan has consistently had low hospital utilization rates (290 to 340 hospital bed days per 1,000 enrollees). This compares with rates of 350 for Group Health Cooperative of Puget Sound and 479 for Blue Cross of Washington state for similar groups of enrollees. Blue Cross nationwide has had 700 to 750 bed days per 1,000 during this same period. Correcting these figures for age and sex does not account for the differences. Both lower admission rates and shorter length of stay contribute to the difference between UHC and Blue Cross. These low hospital utilization rates are the reason that only one out of three dollars goes to hospitals, leaving two thirds to pay for ambulatory care.

This plan also redistributes professional fees. Under the United Healthcare plan about 50 percent of the dollars paid to physicians are paid to primary care doctors as they are in most prepaid HMO plans. This is contrasted to the situation in more traditional Blue Cross-Blue Shield plans where about a third of the professional fees go to primary care physicians and two thirds are paid to specialists.

Discussion

There are several lessons that have been learned by UHC during its first five years. The first and most important is that physicians, when given the opportunity, will participate in programs to control costs in the setting of private practice. Important features of the UHC system that are responsible for widespread participation by primary care physicians are as follows: First, fair reimbursement is made for their own services while putting them in charge of and at risk for the financial outcome for all medical care rendered to their patients. Second, catastrophic cases are removed from this risk-sharing arrangement. Third, participating primary care physicians are helped to learn more about charges of specialists and hospitals without limiting their choice to those that are the cheapest. Education is combined with the financial incentives of the capitated primary care network to allow participating physicians more freedom to balance cost considerations with quality and convenience when deciding where to refer patients and admit them to hospital. This system respects the judgment of each primary care physician and allows him more freedom than plans which require the use of one hospital and a small panel of referral specialists.

By putting primary care physicians in charge

(not allowing patients to self-refer) and then structuring the incentives so that each physician will take an interest in the costs of hospital and specialist care, the plan is able to reinsert fiscal responsibility into the delivery system at the point where it can be acted on by each coordinating physician-decision maker. Individual accounts for each physician are an important aspect of promoting financial accountability. Early in the history of UHC large groups of physicians were at risk for the outcome of the financial account. Those physicians who were interested in maximizing the efficiency of their delivery system were discouraged by colleagues who were part of the same risk-sharing account but remained uninterested in delivering more cost-effective care. The plan evolved into one which contracts with each individual physician (even if they are part of a group practice). This feature, more than any other, allows the physician to be aware of and accountable for the costs of care for his panel of patients.

The plan also has recognized the importance of involving the hospitals and the specialists in efforts to control costs. Initially, primary care physicians were left to discover the costs of various procedures and charges of specialists and hospitals through the process of reviewing referral bills before authorizing them. The participating physician had neither the time nor interest to educate himself about these issues. More recently efforts have been made to publish on a regular basis the average rates for common surgical procedures, for consultation fees, hospital rates, x-ray procedures and drug costs. This allows a primary care physician to compare average costs in the area with the amount being charged by his referral specialists, hospitals and pharmacies. Efforts are currently underway to involve specialists in cost control by enlisting their participation in a referral network of physicians who will cooperate with the primary care doctors in promoting ambulatory surgical procedures and outpatient diagnostic workups. Hospitals have also been brought into the effort to control costs by negotiating a per diem reimbursement rate and allowing them to be at risk for excess expenditure over the per diem. Thus, opportunities are being created for primary care doctors to voluntarily structure a more efficient delivery system.

The primary care network concept provides a viable model which can surmount some of the drawbacks of the traditional closed-panel HMO's. It is flexible and does not require large start-up costs. It is, therefore, the only type of HMO that is suitable to rural areas. It insures access to a primary care physician and thus holds down emergency room use for inappropriate reasons. It is more acceptable to patients than closed-panel HMO's because it allows a wide range of choice of both primary care and specialty physicians. Because of this advantage it should grow much faster than the more traditional closed-panel HMO's.

The most important ingredient in the success or failure of an alternative delivery system such as the primary care network is the level of involvement and commitment of the participating physicians. In the UHC system, unless the primary care physician educates himself and includes monitoring and control of costs within his domain, the plan cannot succeed. The educational effort and the incentives in this system are important stimuli to assist the change but cannot make it occur. In spite of those stimuli many physicians remain resistant to accepting control of medical costs as an important enough task to deserve their time and energy.

It is difficult for a physician to accept this task as worthy of his time and energy. In most instances he is busy enough taking care of patients without also having to worry about controlling the cost of that care. Sometimes cost considerations run counter to quality considerations, which makes it more difficult to balance quality and cost. Unfortunately the primary care physician is the only person with the knowledge to carry out that task in a competent and equitable manner. It is difficult for government or insurance companies to address issues of quality and cost except by large scale approval or denial of categories of care (renal dialysis or cosmetic surgical operations).

Even after a physician does accept his new role as the coordinator-decision maker in the UHC system, he cannot always have an impact on costs. From the physician's point of view there are many things in the medical delivery system which he does not control. For instance, when his patient has a myocardial infarction (MI) there is a standard protocol of good care to follow. The costs of that hospital care cannot be avoided because the physician cannot influence, except indirectly, whether or not his patient will have an MI. In this example the physician control will

happen only at the margin (when the physician is deciding whether to keep the patient in the hospital seven days or ten days for an uncomplicated MI).

There are many elements of medical care which represent expensive but high quality advances in diagnosis and therapy that are worth the charges made for them. There are other new technologies that have no perceptible impact on either morbidity or mortality. It is in this latter area where a well-educated and motivated primary care physician can have an impact on total costs of health care. By educating himself and adhering to firm criteria for carrying out expensive procedures such as coronary angiography, colonoscopy and computer-assisted tomographic (CAT) scanning, he can screen patients very intelligently and cost-effectively for the specialist. However, he must take his role as coordinator seriously in order not to be intimidated by those who have no interest in controlling total costs and therefore promote more widespread applications of new technologies. The primary care network gives private practice physicians a framework in which to begin to control the costs of medical care from within the profession rather than living with increasing amounts of arbitrary regulation and legislation, which might control costs but at great expense to the freedom now enjoyed by the profession.

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Containing Health Care Costs

A Critical Test of the Public-Private Joint Venture in Health

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As the federal government shifted from its traditional roles in health to the payment for personal health care, the relationship between public and private sectors has deteriorated. Today federal and state revenue funds and trusts are the largest purchasers of services from a predominantly private health system. This financing or "gap-filling" role is essential; so too is the purchaser's concern for the costs and prices it must meet. The cost per person for personal health care in 1980 is expected to average $950, triple for the aged. Hospital costs vary considerably and inexplicably among states; California residents, for example, spend 50 percent more per year for hospital care than do state of Washington residents. The failure of each sector to understand the other is potentially damaging to the parties and to patients. First, and most important, differences can and must be moderated through definite changes in the attitudes of the protagonists.

LEST THERE BE any doubt, we have been and will continue to be a nation whose health care delivery system is substantially private but whose health care financing system is substantially public. This confluence of public financing and private delivery, when understood, helps explain much of the bitterness, misunderstanding and unhappiness that have characterized public and private sector relationships in recent years.

Your author has experienced the professional joys and agonies in both sectors. In this paper I borrow extensively from materials presented in 1979 at the University of Chicago and Harvard University, where I argued that the American people have sought from their government assurances that there would be reasonable access to health care services of good quality regardless of individual economic circumstance. Contrary to conventional wisdom, the professionals and the institutions that can provide these valued human services are, in large measure, I believe, fully committed to that goal. And indeed, I believe most but not all providers are willing to address this goal with a recognition that affordability—mainly costs and the containment of costs—is one vital, indeed integral element in achieving this important national value.

To this end this paper prescribes and accepts a legitimate role of government in health care, highlights cost trends that are important, suggests strategies of more effective collaboration between government and the private sector, and urges greater understanding and responsiveness on the parties that can most wisely deal with health care costs, the private health care organizations and most particularly, private physicians and surgeons whose decisions most directly influence total health expenditures.

The Public Role

A brief historical perspective may be a useful reminder that government has played an active,

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vigorous role in the development of our public and private health care system. In the health sector, government intervention began early with the acceptance of responsibility for public health and the establishment of Public Health Service hospitals. The need for protecting the public's health and safety was obvious and so, too, was the need to provide public health agencies with police powers. Few have challenged this obligation of government.

Following World War II the federal government began extensive funding of hospital construction grants, the first of several "capacity building" activities in health that it undertook over the next three decades. The Hill-Burton Act was an early warning signal that government was shifting toward improving access to acute care services, well-dispersed in small hospital units and presumably attractive to practicing physicians. Congressional proponents concluded that acute care hospitals, under private, voluntary, nonprofit community auspices, would be the cornerstone of community health services. Improving distribution of care by adding private sector capacity became a rational and respectable use of general revenues.

Improving access by building capacity and protecting the public health were two interventions firmly rooted in societal values. So, too, was another notion—the development of the National Institutes of Health (NIH) with the concomitant decision of American political leadership to support biomedical research at high federal funding levels. There was a desire to foster scientific resource development and to maintain international preeminence in science. Stimulating biomedical research was good politics since the flow of achievements, particularly in the post-World War II decade, was quickly transferable to the public welfare.

Charles Schultze, before his current chairmanship of the Council of Economic Advisors, observed that it is never easy but at least possible "to reach consensus on matters involving basic values."[1] In the cases of Hill-Burton and NIH, the political lines were drawn naturally and cleanly because they did involve basic values. "As society has intervened in ever more complicated areas, however, and particularly as it aims to influence the decisions of millions of individuals and business firms, the critical issues have a much lower ideological and ethical content."[1(p89)] The current arguments over energy policy, gasoline rationing and national health insurance are excellent examples of complex policy issues, each with strong countervailing ideologic elements.

Moving from public consensus for hospital construction and bioscientific research to a political consensus for public financing of privately rendered personal health services was more contentious. It took more than two decades to reach a consensus to assist the aged of the nation in meeting their costs of health care. The passage of Titles XVIII and XIX of the Social Security Act depended upon two conclusions that eventually came to dominate the debate. The first was the promise of independence and security for our elderly. The aged could not afford the financial insecurity of major illness (nor could the poor). The second was the conclusion that government had the capacity to manage a carefully planned health insurance program in spite of the incredible range of critical details, the well-orchestrated opposition by certain essential providers and the overall enormity of the task.

The decision to proceed with federal financing for the aged and poor, and eventually the chronically disabled, "the gap-filling" role, contained several important assumptions:

- Medically necessary benefits under the program would be physician-ordered services that relieved discomfort and improved personal health status.
- Public programs would be administered by private insurers in a manner that mirrored their private business. Hospitals would be paid reasonable costs, the common Blue Cross method, and physicians would be paid the lower of their usual, customary and prevailing (UCP) charges to all of the patients.
- Provider participation and beneficiary understanding would take priority over cost.

Some extra administrative latitude was granted to states which contributed matching funds for the care of the poor and medically indigent within their state boundaries.

In 1970 and again in 1972 signs of congressional discontent over cost and quality began to appear. No longer was provider participation a major concern. Physicians and hospitals and thousands of other providers were caring for public beneficiaries at increasing cost to the public treasury. The 1970's saw the birth of health planning, Professional Standards Review Organizations, fraud and abuse units, and reimbursement

ceilings. These statutory changes were among dozens that passed and were sent to the Department of Health, Education, and Welfare (DHEW) for implementation. Many provisions, too difficult politically to settle in Congress, were left to the discretion of the DHEW Secretary.

We health professionals tend to overestimate the level of debate and understanding that is reached in legislative formulation. We want to believe that the legislative process is a deliberative, inquiring and thorough examination of the substance of every phrase, and that the authors themselves are entirely clear in their intent. We believe the consultative process, through public hearings and direct discussion, will assure that legislation is wisely framed, at least before political compromise is imposed. Victor Fuchs, one health economist who has shown some skepticism toward the value of the medical care system in raising the nation's health status, has stated very clearly his conclusions on governmental interventions:

> In my view, National Health Insurance and other governmental interventions in health are best viewed as political acts undertaken for political and social objects relatively unrelated to the health of the population. This seems to be an inescapable conclusion from the evidence now available.[2]

Perhaps now it is clearer why hospital cost inflation was a highly politicized issue for DHEW from 1977 through 1979. The Secretary, recognizing the legislative climate, knew that cost containment legislation could not pass unless the public and their elected representatives reached a collective "political" conclusion that costs were unbearable and out of control. Until that happened the technical details of the proposed law as to whether inefficient hospitals were to be rewarded, whether hospitals had due process, and whether DHEW had too much administrative latitude, were sufficient to thwart the legislative proposal in one house of Congress.

It is not enough to have a technically solid bill. There has to be a serious and believable issue that a majority of congressmen feel certain can be remedied by law. Identifying those issues and having confidence that there are real remedies has led to a stagnated legislative agenda in the current Congress, much to the relief of those content with the status quo.

So far I have identified three roles of government: the public health and safety role, the capacity building role, and the gap-filling financing role of allocating general revenues and payroll taxes to assure needy groups baseline health care purchasing power. It is the latter role that some believe has placed onerous and unreasonable harassing strings on government health care purchases.

Americans have expected other activities from their government. These include the following:

- *Government as a data gatherer and information dispenser.* This role extends well beyond essential census and vital statistics data. Every major industry, including the health industry, uses government-produced or government-commissioned data.

The growth of informed consumerism in health depends as well on a public familiar with good personal health practices, a public that can comprehend and compare health insurance options, and that is equipped to understand the limits of medical care. As is the case with so many government roles, this is not an exclusive or a preemptory responsibility, but one to be shared with nongovernmental enterprise. Publication of nutritional standards by DHEW and the American Cancer Society's recommendations for preventive checkups are two recent examples of public-private initiatives to inform the public.

- *Government as an experimenter, a demonstrator and an agent of change.* Surely this has to be one of the most useful and innovative roles for government. Health services research, encouraging productivity in the delivery of health care, and experiments in new forms of reimbursement, require federal funding and objective evaluation by dispassionate social scientists. Only those entirely satisfied with the status quo will challenge that as a legitimate public responsibility.

- *Government as a private market protector and stimulator.* For those who lament the vast regulatory machinery that has characterized government's interventions in almost all fields of endeavor, it is paradoxical to suggest that free market preservation is a public responsibility. Yet in almost every aspect of our economy the free and unfettered market depends upon antitrust, antimonopoly legislation to insure the maintenance and growth of a price sensitive marketplace. Curiously, the choice in public policy is not between regulation and nonregulation in health; it is a choice between one form of intervention and another.

In sum our government does have multiple responsibilities in health. Many, including myself, feel these government roles are real, necessary and right for a compassionate, progressive society. What is more debatable is how well these roles are implemented, and whether the government has the demonstrated capacity to fulfill them. Nowhere is the issue more crisply encountered than in the role of financing care for those citizens and residents who cannot meet the costs themselves—the "gap-filling" role.

The Costs of Care

Between 1965 and 1978 national health care expenditures rose at a compounded annual rate increase of 12.2 percent while the gross national product (GNP) rose at 9.0 percent. During the same period public financing of those expenditures rose from 25 percent to 41 percent. Total per person expenses for personal health care rose from $188 per year to $753; in 1980 each person will be spending at the rate of $950 per annum.[3]

Certain responses to these statistics are as predictable as they are painful:

- "What's wrong with a public that spends for health care? Americans simply want more health care and less of other goods and services."
- "Who *knows* what the right health care expenditures percentage of GNP ought to be? And what right have bureaucrats to impose their views?"
- "Everything is escalating—oil, mortgages, etc. Government dollars and patient demands are the culprits in rising health care costs."
- "Hospitals and physicians are ripping off the system, overcharging for many useless or ineffective services."
- "It's technology and defensive medicine. Blame the scientists and the lawyers."

These kinds of responses reflect a sampling of the division within the ranks of buyers and sellers of health services. *They also reflect the disagreement over whether there is in fact a cost problem.* If health costs are not a serious problem, there is little reason to blame any one factor or to find palliatives or cures to problems that do not exist.

To this observer the issue is not whether

- There should be a limit on the GNP share for health (there should not).
- Technology adds costs (some does and some does not).
- Physicians provide unnecessary care (some seem to provide much more care than others; most care is probably effective and necessary).
- Over-bedded hospitals add costs (they do).

The real issue is whether the American taxpayer —you and I—can persuade other American taxpayers that health care in 1980—a substantial part of which government must purchase—is worth the estimated $950 per person. And second, whether we can afford at that average cost to pay for 23 million Americans on Medicaid; and three times that average for the 27.5 million Americans on Medicare who are elderly or chronically disabled.[4]

If the answer is that we cannot easily afford those commitments and perhaps some additional relief for 8 to 10 million Americans at or below the poverty line who have no health insurance, then my view is there *is* a cost problem. If we must begin to sacrifice other valued public services—national defense, aid to education, bioscientific and high energy research, police and fire protection as examples—to guarantee health care entitlements, reasonable persons can only conclude that cost and value in health care are real, rational and very serious public policy problems.

These difficult issues come at a time when the Congress and many states, with a mandate to contain inflation and reduce public expense, must necessarily confront every major item of expenditure. In California, as in many states, the largest single expense is the Medicaid program (Medi-Cal). As is true in all governments, health expenses are running faster than revenue growth. At the federal level we are now spending one of every nine dollars on health care, and that is before 1980 budget cuts for every health program except the Health Care Financing Administration. The task of persuading the private health sector that costs of care are reaching beyond the means of our various governments' abilities to finance health services has often been met with the cry of political overpromise. A more helpful response would be to ask "How can we help? Can costs which are already high be contained? Is the Voluntary Effort (VE) of our major associations a sufficient awakening and response to the cost problems, or can we do better?"

Government, as the single largest purchaser of health services, believes we can do better. It contends that the rate of cost escalation can be

TABLE 1.—*A Comparison of Hospital Costs and Activity in Washington State and California, 1977*[6]

	Washington	*California*
Beds/1,000	3.3	3.8
Occupancy rate (percent)	66.1	66.1
Average length of stay (in days)	5.5	6.6
Admissions per 1,000 population	146	141
Per capita personal income	$7,528	$7,911
Expenses per stay	$1,099	$1,610
Expenses per day	$ 200	$ 246
Expenses per capita	$ 180	$ 260
Expense per capita as a percent of per capita income	2.5	3.4

moderated, not eliminated; in fact moderated further with no loss of quality. The three important allies government needs to effect that ideal are private medical practitioners, health care institutions and informed consumers of health services. The Voluntary Effort is one organized activity that has attempted to form a coalition to moderate costs. Its backers feel that government has not been supportive and, in fact, is skeptical that this effort at self-regulation has had any profound effects on lowering the rate of escalating hospital expenses. Surely we can agree on one aspect. VE was as important as any other single factor in organizing opposition to cost containment legislation and staving off new legislative injunction. Whether the short-term decline in hospital expenditure growth can be attributable to voluntary regulation or state rate review or both, hospital cost increases in 1979 were no longer the aberrant performer in the Consumer Price Index (CPI).

The Voluntary Effort, well motivated as it is, does not address the deeply rooted controllable causes of health care inflation. In a sense the danger of the Voluntary Effort is the probability that it will be the private sector's singular response to rising expenditures. Even in 1978 when hospital expenses rose less than 13 percent and Medicare fees were controlled by a special economic index at less than 6 percent, Medicare costs rose 15 percent from $22.5 billion to $25.9 billion.[5] Of that, Medicare physician services expenditures went from $4.6 billion to $5.5 billion or 16.4 percent. Increases in the number of Medicare beneficiaries from approximately 26.4 million to 27 million account for only a fraction (2.2 percent) of the rise in costs. Is the Voluntary Effort enough? Probably not.

Does the Voluntary Effort seek out differences in hospital costs among states? Not yet. A 1977 comparison of hospital costs and activity in the states of Washington and California (Table 1) is illuminating.[6] Why should hospital expenses in California be so much higher? A 1978 comparison is even more striking. Hospital per capita expense per year or annual per capita hospital expense in Washington was $201; in California, $302—50 percent higher.[7]

These wide ranges in costs suggest that much remains to be done in explaining and indeed, in eliminating unnecessary hospital costs. These extraordinary variations suggest that medical practice patterns may be quite different in the two states. If in fact they are, is it unreasonable that payers in California would want to know what more in benefits they are gaining from their expenditures in California hospitals? Is it unreasonable for Social Security beneficiaries in the state of Washington to ask why so much more of their Trust Fund contribution should be directed into California or other high per capita cost states?

Next Steps

Can there be accommodation between public payors and private care givers in an effort to temper costs? Is it conceivable that what on the one hand is an inherently adversarial relationship between buyer and seller, can be a creative and constructive partnership on the other? The answers are not easily forthcoming. We have sunk to a low point in goodwill between the public and private sectors and a new high in tension and mistrust among the parties. Moreover, the health field is more massive in its dimension and more disparate in its outlook than ever before. Regional surpluses in health and medical manpower are almost as common as current shortages, creating different kinds of insecurities and a new set of economic pressures. How government beneficiaries, the high-risk poor and aged, will fare in a world competing for the healthy patient is quite unclear.

Despite this environment I believe we can get on track to restore reasonable public-private sector relationships. It is essential to do so for there will be an ever increasing interdependence between public dollars and responsive private providers. That suggests to me that the present commitment to intransigent opposition by both parties is not only misguided but dangerous. No one, least of all me, expects two natural adversaries to enjoy wholly common interests and mutual goals. Neither buyer nor seller can invoke "the public interest" as his sole domain.

Failure to achieve mutual compatibility invites the political right of the private provider sector to withdraw and serve only the employed and the wealthy. The growing conservatism of big labor adds plausibility to the prospect. Failure to achieve mutual compatibility invites the political left to push for separate government-operated and directed health organizations. It also encourages more "command-control" regulations upon an embattled private industry. None of these eventualities would be correct for the American public.

The first step—indeed the next step—is to moderate the attitudes of the protagonists. If there is any crisis in health care, it is the lack of private sector understanding of the national condition and government's increasing diatribe against the care givers. The private sector must remind itself constantly that the health care of more than 50 million Americans is financed substantially by government. As the population ages and gaps are filled, the number will increase—I hope not too much. Taxpayers, you and I, and contributing beneficiaries expect that government spending will be prudent and tight, and that at the very least, no blank checks will be issued. We also expect that government will not enrich its contractors unreasonably. The national condition is that government must pay billions for services while simultaneously stimulating efficiency in the health system from which it is purchasing. The private sector must recognize the legitimacy of government's public responsibility and stop resenting its preoccupation with cost, value and quality assurance.

A change in government's attitude is also in order. Federal officials have no appreciation of the "lead-hand" image they have created and the rancor that is caused by endlessly ballyhooing fraudulent practices and health systems deficiencies. Government should engage, not constantly inflame, an industry that can help. If we have inflationary reimbursement and payment programs —and we do—let us deliberate together with industries and professionals in search of viable alternatives. Hospitals, for example, feel that government is castigating them for bed surpluses and poor occupancy. Yet government surely shares the responsibility for the nation's bed supply. Government and health politics are now inextricably entwined, with the result that political opportunism is molding some unfortunate government attitudes. A little old-fashioned high-minded statecraft might restore some order. Most health professionals and hospitals are willing and able to improve our nation's care. Government ought to be willing to accept that assumption. Then, we could begin to whittle away at questionable services and expensive redundancy. We could start real initiatives in reimbursement reform, quality enhancement and health promotion.

In 1972 Anne and Herman Somers wrote:

> We do not have to abandon all of the assets of private initiative to obtain the advantages of governmental financial strength, social equity or democratic control. Nor is it necessary to bind the hands of government to harness the capacities of the private sector in the public interest. We can assimilate both to mutual advantage.[8]

This is where I land. The virtues of both the public and private sectors in health must be discovered and fully savored. There are public and private responsibilities in health care that can only be met through the combined strength of public financing and private care givers. It is not too late for the key players, government and private care providers, to realize that simple but currently elusive fundamental.

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Antihypertensive Pharmacology

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Although drug treatment of hypertension is associated with improved survival and decreased vascular complications, drug compliance is a major problem in the control of hypertension. All antihypertensive medications are associated with side effects; thus, it is a physician's responsibility to explain to each patient the side effects of the drugs he prescribes to treat hypertension, and to instill in the patient a sense of necessity for the treatment of hypertension. The choice of antihypertensive drug should be made based on each patient's lifestyle, overall health and ability to tolerate the drug. Ideally, the antihypertensive regimen should be simple, effective, convenient to take and have very few side effects.

HYPERTENSION IS A silent epidemic of the 20th century. According to the National Health Examination Survey of 1960 to 1962, 15 percent of whites and 27 percent of blacks had hypertension based on the World Health Organization criteria (blood pressure above 140/90 mm of mercury).[1] Despite availablity of adequate treatment, most hypertensive persons have inadequately controlled blood pressure. Both a lack of awareness and lack of compliance contribute to the problem.[2]

The mortality associated with hypertension and hypertension-related myocardial infarctions, cerebrovascular accidents and renal failure account for more than a million deaths per year in the United States.[3] In addition, the morbidity associated with these diseases has been estimated to cost more than $5 billion a year.[3] It is clearly less expensive to treat hypertension, both from a financial and an emotional viewpoint, than to deal with its consequences. In view of the Veterans Administration Cooperative Study, which shows that control of blood pressure does prevent some of the catastrophic consequences of prolonged hypertension,[4-6] there has been an increasing effort to educate both physicians and patients to detect and control high blood pressure.

The definition of hypertension is arbitrary because blood pressure in any population is a continuous variable. Actuarial data show that elevated blood pressure shortens life span, but what is startling is that the increased mortality begins with persons in the normotensive range.[7] Therefore, one can argue that the lower the blood pressure, the better will be the expected longevity. In the United States a blood pressure of 120/80 mm of mercury is the mean for the age group between 18 and 24 years, and this number increases with advancing age.[8] Elevation of blood pressure with advancing age is not universally seen, however, but seems to be part of our Western culture.[9] Therefore, because any definition of

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hypertension is arbitrary, it should be interpreted within each population group. Most physicians would agree that a blood pressure of 150/100 is definitely in the hypertensive range and requires some sort of treatment. With people under 40 one could argue that a blood pressure above 140/90 mm of mercury would warrant treatment, although good evidence is lacking that treatment of blood pressures in this borderline range will reduce organ damage and prolong life. Both systolic and diastolic blood pressure elevations are important in predicting morbidity and mortality from hypertension, although in most people both numbers tend to move in the same direction.[10,11] Isolated elevation of the systolic pressure is probably significant because there is retrospective evidence that elderly people with only systolic blood pressure elevation suffer increased mortality compared with normotensive controls.[12]

The physiologic basis for essential hypertension is elevated peripheral resistance. Cardiac output is usually within normal limits. Only in a small minority of hypertensive patients is increased cardiac output the cause of hypertension. This subgroup of hypertensive patients tends to be younger and has a more labile pattern of blood pressure elevations.[13-15]

The cause of most forms of hypertension is unfortunately not known. There is a likelihood that essential hypertension has multiple causes, although evidence to support this is lacking. Measurements of renin activity in hypertensive patients has received considerable attention recently, but categorizing patients by their renin levels has not improved blood pressure control and, at present, merely adds to the already skyrocketing cost of medical care.[16-21]

When a physician sees a new hypertensive patient, he or she must decide the extent of the workup necessary to exclude secondary causes of hypertension. Some 95 percent of hypertensive patients have essential hypertension and need medical therapy to control their blood pressure. By far, the majority of patients with *correctable* hypertension will have renal artery stenosis, whereas pheochromocytoma and primary hyperaldosteronism are rare. However, if the history or physical examination specifically suggests pheochromocytoma, a physician should not hesitate to measure urinary levels of catecholamines, vanillylmandelic acid, or both, because surgical operations for these patients can be lifesaving. If serum electrolytes indicate hypokalemia and alkalosis in an untreated hypertensive patient, a workup to exclude primary aldosteronism is warranted.

TABLE 1.—*Choice of Drugs in Treating Hypertension*

Diuretics
thiazides
furosemide
spironolactone
Beta-adrenergic blocking agents
propranolol
metoprolol
Central sympatholytic drugs
clonidine
methyldopa
Peripheral sympatholytic drugs
guanethidine
reserpine
prazosin
Drugs that affect vascular smooth muscle to decrease peripheral vascular resistance
hydralazine
minoxidil
diazoxide
sodium nitroprusside

The exclusion of renal artery stenosis is more difficult. The only way to absolutely exclude this disorder is by renal angiography. However, doing renal angiography on a mass scale is impractical, and intravenous pyelography will be falsely negative 30 percent of the time. Therefore, mass screening for this form of hypertension is not possible. Nevertheless, the presence of certain clinical features warrants renal arteriography. Severe hypertension in a young woman who has had no family history of hypertension should arouse a strong suspicion that fibromuscular dysplasia in one of the renal arteries may be the cause of the hypertension. A continuous abdominal bruit without any other signs of arteriosclerosis in a hypertensive person should also indicate the possibility of renal artery stenosis. Finally, anyone with normal renal function and severe hypertension that is poorly responsive to antihypertensive therapy may be a candidate for renal angiography to rule out renal artery stenosis.[22-24] In addition to the above-mentioned secondary causes of hypertension, coarctation of the aorta is a rare but easily diagnosable cause of hypertension which should never be missed if care is taken to measure blood pressure in both the upper and lower extremities.

Once a physician decides to treat a patient's hypertension medically, one of many drug regi-

mens may be chosen (see Table 1). Any drug or combination of drugs that is effective and convenient to take, and causes minimal side effects, is satisfactory.

Drugs in the Treatment of Hypertension

Diuretics

There are two types of diuretics that have been most used in the treatment of hypertension. Thiazide diuretics impair distal tubular sodium reabsorption in the kidney and loop diuretics inhibit chloride reabsorption at the ascending limb of the loop of Henle. In patients with normal renal function, both drugs lower blood pressure, but because thiazides are much cheaper and probably more effective, they have become more popular.[25-27]

The mechanism by which diuretics lower blood pressure is disputed, but the fact that they work is not. Severe sodium restriction will by itself lower the blood pressure in most hypertensive patients.[28] It is reasonable to assume that the diuretics alter salt and water balance in such a way that blood pressure is lowered. During acute diuretic therapy the blood volume and cardiac output is lowered to decrease blood pressure, but with chronic therapy the cardiac output returns to normal, peripheral resistance falls, and there is only a small but persistent reduction in extracellular water and plasma volume.[29,30] It is unlikely that thiazides have a direct vascular effect on lowering blood pressure because in neither isolated arteriolar preparations nor in anephric animals do thiazides have any vascular effect.[31]

The major side effects of diuretic therapy include hyperuricemia, hypokalemic alkalosis and hyperglycemia. Hypokalemia is usually mild and does not require specific therapy unless the patient is also taking a digitalis preparation.[32] Thiazide diuretics have been associated with elevation of serum lipids, the consequences of which are still speculative.[33] Rare allergic reactions to both thiazides and loop diuretics have been described. Reversible hearing loss has been associated with high doses of furosemide.

The aldosterone antagonist spironolactone has been used in treating hypertension. It has been postulated that spironolactone is effective in "low-renin" hypertension because the subset of patients with this condition have excess mineralocorticoid activity unrelated to aldosterone. However, hydrochlorothiazide works as well as spironolactone in hypertensive persons with low renin levels, and produces fewer side effects.[34]

For most hypertensive patients, the diuretic of choice is a thiazide. However, in patients with renal failure furosemide may be necessary to achieve a diuresis and hypotensive effect. If severe hypokalemia results from diuretic-induced secondary hyperaldosteronism, the use of spironolactone or triameterene should cause some potassium-sparing activity.

The Beta-Adrenergic Blocking Agents Propranolol and Metoprolol

Propranolol has become popular recently as an antihypertensive agent; however, its mechanism of action is not understood. Both propranolol, which blocks the β_1 (cardiac) and β_2 (vascular, bronchial) adrenergic receptors, and metoprolol, which predominately blocks the β_1 adrenergic receptors, have been shown to lower blood pressure in experimental animals and in humans.[35,36] Because selective β_2 antagonism has not been shown to lower blood pressure,[37] it appears that inhibition of the β_1 adrenergic receptor is responsible for lowering of blood pressure. Although some researchers have suggested that propranolol lowers blood pressure because it decreases plasma renin activity, there is substantial evidence against that being the only explanation.[38] Propranolol, when given chronically, lowers renin activity after the first dose, but the hypotension may not occur for as long as a week after the initiation of therapy.[39] Propranolol, when given intravenously, lowers renin activity immediately but the blood pressure does not decrease.[40] Practolol, another beta-blocking drug, has been shown to lower blood pressure without lowering basal plasma renin activity.[41]

Although other hypotheses have been put forth to explain propranolol's effect on lowering blood pressure the most consistent explanation is that it does so by decreasing cardiac output. The physiologic sequences after administration of propranolol are as follows: there is an immediate decrease in cardiac output but an increase in peripheral vascular resistance such that blood pressure does not change. The change in peripheral vascular resistance over several weeks readjusts close to baseline so that the chronic decrease in cardiac output results in arterial hypotension.[42] Because not all people respond to beta-blocking doses of propranolol in the treatment of hyperten-

sion, there is no one clearcut explanation for the mechanism by which beta-blocking agents lower blood pressure.

Propranolol by itself can be used to control blood pressure, but an additive effect has been observed when used together with a diuretic or a peripheral vasodilator, or both.[43,44]

The pharmacokinetics of propranolol are complex and have been reviewed recently.[45] Some 40 percent to 70 percent of the drug is extracted by liver before systemic availability; thus, there is a large variation among patients in the drug levels achieved after a standard dose.[46] Because measurements of its presence in the blood are not readily available, looking at decrements in tachycardia on exercise may be a reasonable way to evaluate the extent of beta blockade. The half-life of the drug is usually four to six hours, but its hypotensive effect can last much longer. It has been possible to give propranolol twice daily or even once daily without compromising blood pressure control.[47] Side effects of propranolol include heart failure, atrioventricular block, hypoglycemia, asthma, central nervous system disturbances and peripheral vascular compromise. In addition, propranolol blocks some of the warning signs and symptoms of hypoglycemia; therefore, its use may be contraindicated in insulin-dependent diabetic patients. The severe cardiac and pulmonary side effects of propranolol generally occur in patients with cardiac disease or underlying pulmonary disease and may occur even after they take a small dose. The most common complaint of patients taking propranolol is that they become easily fatigued after exertion, but usually the side effects are not incapacitating.[48] All of these side effects are the result of beta-adrenergic receptor blockade in the various tissues.

Generally, the hypotensive dosage of propranolol ranges between 160 and 640 mg a day, which may be given in two divided doses. It is important for practicing physicians to realize that the cardiac effect of propranolol is almost immediate, but the maximum hypotensive effect may take several weeks to achieve. This knowledge will avoid needless changes in drug dosages or the addition of another antihypertensive drug before a maximal response to propranolol is achieved.

Metoprolol has been released recently on the market in the United States. The drug has selective β_1 action although in very high doses it will also cause some β_2 blockade. The drug is an effective antihypertensive agent with potency comparable to propranolol. Metoprolol may be tried in hypertensive patients with asthma, but only when other drug therapy is not possible.

Central Sympatholytic Drugs

Clonidine. This is a centrally acting antihypertensive drug that was initially developed as a nasal decongestant. At present, there is a debate as to the exact mechanism of the action of clonidine, although most researchers agree that the drug's effect is related to its alpha-adrenergic agonist properties.[49] When given acutely clonidine produces alpha-adrenergically mediated vasoconstriction. However, clonidine also inhibits sympathetic outflow from the central nervous system and increases the depressor effects of baroreceptor stimulation.[50-60] This biphasic effect of the drug is best seen in an overdosed patient where the initial response is hypertension followed by a more prolonged hypotension due to inhibition of sympathetic outflow from the central nervous system.[53]

Because of the reduced sympathetic activity, clonidine lowers blood pressure by decreasing both cardiac output and peripheral resistance. The pharmacokinetics of clonidine indicate that the drug has a half-life of about 12 hours and its duration of action is also about 12 hours, although the range for both variables can span from 6 to 24 hours.[54,55] The drug is effective in lowering the blood pressure when combined with a diuretic to prevent salt and water retention.

The main problems with clonidine are the disturbing side effects to the central nervous system that include sedation and inability to concentrate. Dryness of the mouth secondary to decreased saliva flow is very common. The incidence of impotence is probably similar to that observed with other central sympatholytic drugs.[56] The drug ordinarily does not cause orthostatic hypotension, but orthostatic hypotension can occur if the patient is dehydrated.

Among the most serious side effects described for clonidine are rebound hypertension and signs of sympathetic overactivity 8 to 36 hours following sudden withdrawal of the drug. Elevated serum and urinary levels of catecholamines also have been noted in clonidine withdrawal.[57,58] Because the incidence of withdrawal is not known, a physician prescribing the drug should inform the patient about the danger of sudden cessation of therapy. If use of clonidine must be discon-

tinued, a regimen involving tapering the drug dosage over several days to a week is desirable. If rebound hypertension occurs, it can be treated by reinstituting clonidine.

The usual dosage of the drug is 0.2 mg to 1 mg a day in two divided doses. However, if the patient is experiencing withdrawal symptoms during the dosage interval, clonidine may have to be given three or four times per day. The hypotensive effect of clonidine is reversed with the use of a tricyclic antidepressant.[59] This interaction occurs probably at the central alpha-adrenergic receptor level.

Methyldopa. Methyldopa is also a centrally acting antihypertensive agent whose mechanism of action is incompletely understood. Present evidence indicates that the drug has to be metabolized to α-methylnorepinephrine in the brain to be effective.[60] In turn, α-methylnorepinephrine interacts with central alpha-adrenergic receptors to decrease sympathetic outflow.[61] Methyldopa, like clonidine, decreases blood pressure by reducing both the cardiac output and peripheral resistance.[42] The oral absorption of the drug is probably through an amino acid transport system in the small intestine. Absorption is incomplete and varies from 50 percent to 80 percent.[62,63] The plasma half-life of the drug is only one to two hours, but its hypotensive effect can last as long as 24 hours, probably because the active metabolite α-methylnorepinephine has a long half-life in the brain.[64] The drug has to be used with a diuretic to avoid salt and water retention secondary to decreased blood pressure.

As with clonidine, a major side effect involves depression of the central nervous system, including drowsiness, decreased intellectual drive and forgetfulness. Impotence and dryness of the mouth also are seen with the chronic use of methyldopa.

A positive direct Coombs test will develop in about 25 percent of persons on long-term methyldopa therapy, which in itself is harmless, except for difficulty in crossmatching blood for transfusions.[65] However, in 1 percent to 5 percent of patients with Coombs test positivity secondary to methyldopa, hemolytic anemia will develop, which will necessitate the cessation of the drug. In addition to hemolysis, the use of the drug has been associated with fever and hepatic dysfunction that can resemble either acute hepatitis or chronic active hepatitis.[66] With the removal of methyldopa there is usually complete reversal of the hepatic abnormalities, although hepatic failure has been reported.

The usual dosage of the drug is 500 mg to 2.5 grams a day in two divided doses, although the drug can be administered once per day with good blood pressure control.[67] Raising the daily dosage of methyldopa beyond 2.5 grams is not associated with an enhanced hypotensive response. The drug is a reliable antihypertensive agent with intermediate potency, but not popular with young and active hypertensive patients because of the drug's central depressant effect.

Peripheral Sympatholytic Drugs

Guanethidine. This is a potent antihypertensive agent that has been in clinical use for many years. Because of its basic guanidine group, the drug does not enter the brain and, consequently, it lacks any significant effect on the central nervous system.[68] The drug, transported into presynaptic sympathetic neurovesicles by the norepinephrine pump, depletes the norepinephrine and then inhibits its release, resulting in a functional sympathetic denervation.[69] The drug has complicated pharmacokinetics with an elimination half-life of five days. The therapeutic effect of the drug has been correlated with this terminal phase of elimination.[70,71]

Because guanethidine has to get into the adrenergic neuron to be active, any drug that interferes with the norepinephrine pump will inhibit its hypotensive effect. The tricyclic antidepressant drugs are the most potent in this respect, and can totally reverse guanethidine's hypotensive effect.[72] In addition, phenothiazines, ephedrine, amphetamines and cocaine can block uptake of guanethidine into nerve endings.[73-75]

The drug lowers blood pressure mainly by decreasing cardiac output through a reduction in venous return, an effect which is exaggerated when the patient is in an upright position. The side effects of the drug are secondary to unwanted aspects of adrenergic blockade. Postural hypotension and exercise-induced hypotension can lead to syncope. Diarrhea, retrograde ejaculation and nasal stuffiness are frequent. The drug causes salt and water retention so that concomitant use of a diuretic is necessary.[76] One of the advantages of guanethidine is that it is effective when given once a day. The daily dose varies from 10 mg to as high as 500 mg. Because the terminal half-life of guanethidine is five days, it may take as long as 20 days to reach a maximal

steady state effect. This aspect must be taken into account when the physician decides to increase the dosage of the drug. Because other drug regimens are frequently better tolerated, the use of guanethidine has decreased. However, in refractory cases of hypertension guanethidine has been used with success. Bethanidine is similar to guanethidine except that its much shorter action requires taking it more frequently. Side effects of bethanidine are similar to those produced by guanethidine.

Reserpine. Reserpine interferes with the integrity of the storage vesicles of adrenergic neurons and leads to degradation of norepinephrine by monoamine oxidase.[77] This action results in a pharmacologic adrenergic blockade. The drug readily crosses the blood-brain barrier so that its use is associated with numerous effects to the central nervous system. Reserpine is an antihypertensive drug of intermediate potency. When given orally it takes several weeks to achieve a maximal effect. The advantage of using reserpine is the convenience of once-a-day administration and its low cost. The drug has numerous side effects including sedation and disturbed thought processes. Psychotic depression has been described, especially when higher doses of the drug are used.[78] Nasal stuffiness and dryness of the mouth are common side effects. Reserpine increases gastric acid secretion and may exacerbate peptic ulcer disease. In high doses, reserpine may cause upper gastrointestinal bleeding. Reserpine's association with breast cancer has not been confirmed.[79]

The usual dosage is 0.25 mg once a day. The use of a diuretic is mandatory with reserpine to avoid salt and water retention.[80] As with guanethidine, reserpine should be reserved for patients in whom the use of other antihypertensive drugs with fewer side effects is not feasible.

Prazosin. This drug was initially marketed as a peripheral vasodilator because of its ability to inhibit phosphodiesterase, but it is also a potent postsynaptic alpha-adrenergic inhibitor. Because the in vitro concentration necessary to inhibit phosphodiesterase is almost 1,000 times that required to inhibit alpha-adrenergic receptors, it is more likely that the drug works through its adrenergic blocking properties.[81,82] Prazosin, like other alpha-adrenergic blocking agents, can cause orthostatic hypotension. This effect is especially prominent during the first few doses and seems to ameliorate with continued use of the drug.[83,84] For obscure reasons, prazosin, unlike the peripheral vasodilators, does not stimulate renin or cause reflex tachycardia in the face of lowered blood pressure.[85,86] The use of diuretics is necessary when prazosin is administered over a long time to avoid salt and water retention.

Overall, prazosin is well tolerated and has been found to be a useful antihypertensive drug of intermediate potency. The usual dosage is 2 to 20 mg per day given in two to three divided doses. The plasma half-life of the drug is 2½ to 4 hours, but the duration of effect of the drug is longer than that expected from plasma half-life.[87]

Drugs That Directly Affect Vascular Smooth Muscle

Hydralazine. Hydralazine has been on the market for over 20 years, but its popularity as an antihypertensive drug has had a recent resurgence.[88] The improved acceptance is almost entirely due to the fact that when hydralazine is combined with a beta-adrenergic blocking agent and a diuretic there is no tachyphylaxis. The drug has a direct effect on the arteriolar smooth muscle to decrease peripheral vascular resistance. However, if the drug is given alone, baroreceptor-mediated increases in cardiac output, plasma renin activity, and salt and water retention negate the hypotensive effect of the drug. Hydralazine is well absorbed from the intestine, but approximately 50 percent is metabolized during the first pass through the intestinal wall or the liver. The metabolism of hydralazine is partially under genetic control with slow acetylator phenotypes achieving higher plasma levels than fast acetylators of the drug. Although the half-life of the drug is relatively short (2 to 6 hours), the hypotensive effect can last for as long as 12 hours making administration twice a day possible.[89] The usual daily dose of hydralazine is 50 to 400 mg. The fast acetylators are the persons who may require higher doses of the drug to achieve a good antihypertensive effect.

The side effects of hydralazine are mainly related to the reflex sympathetic changes it produces. Palpitations and tremors can be reasonably controlled with beta-adrenergic receptor antagonists. The drug should not be used in patients with angina because it can preciptate myocardial infarction. The major side effect which limits hydralazine use is its ability to induce a lupus-like syndrome. This occurs more frequently in slow acetylator phenotypes and in patients receiving a

daily dose that exceeds 200 mg.[90] The lupus syndrome is reversible on withdrawal of the drug.[91] The development of drug-induced lupus carries a good prognosis because neither central nervous system symptoms nor renal abnormalities develop.

Minoxidil. Minoxidil is a drug whose mechanism of action is very similar to hydralazine except that it is more effective.[92] The drug has been released by the Food and Drug Administration (FDA) for general use as an antihypertensive agent. Experimental studies in dogs have shown right atrial hemorrhagic lesions after the use of minoxidil, but neither extensive use in humans nor in other animals has resulted in similar pathologic effects.

The drug is rapidly absorbed after oral administration, and plasma half-life is approximately four hours. The effect of the drug, however, can last as long as 24 hours, probably because the drug accumulates in vascular tissues, the site of its pharmacologic effect.[93] The drug is usually given in two divided doses, with dosage varying from 2 to 40 mg a day. As with any peripheral vasodilator, the use of minioxidil is associated with reflex tachycardia and salt and water retention[94]; thus, this drug is most effective when used with a diuretic and a beta-adrenergic blocking agent. Pulmonary hypertension has been described with the use of minoxidil, but in these cases the elevated cardiac output, fluid overload and left ventricular failure contributed more to the pulmonary hypertension than an elevated pulmonary vascular resistance due to the drug. Minoxidil when injected into the pulmonary circulation decreases pulmonary artery pressure.[95]

The major problems associated with the drug have been avid salt and water retention and unwanted hair growth. Salt and water retention can be controlled by the use of potent loop diuretics in most cases, but patients with moderate renal failure occasionally escape the effects of the diuretics. Unwanted hair growth is especially unaesthetic for women, but aside from cosmetic consequences, it has no harmful effect. Minoxidil is an extremely potent vasodilator and will lower the blood pressure in cases where other drugs have failed.[96] The use of minoxidil should be limited to patients who do not respond to conventional medications, until more widespread experience with the drug is gained.

Diazoxide. This drug is an analogue of the thiazide diuretics, but it lowers blood pressure by a different mechanism. The drug is a potent peripheral vasodilator; thus, it lowers blood pressure by reducing the peripheral resistance. Although diazoxide is more commonly given intravenously for hypertensive emergencies, the drug will lower the blood pressure when it is administered orally.

Diazoxide is well absorbed orally and has been used for many years for the treatment of idiopathic hypoglycemia. The drug is about 90 percent protein-bound. Initially, rapid bolus injection of the drug was advocated to get a good hypotensive effect, but recent evidence indicates that this is not necessary.[97,98] The fact that the drug reduces blood pressure when given orally should disclaim any theories that plasma protein-binding needs to be overcome to achieve hypotensive response. There is also evidence that the tissue-binding of diazoxide is reversible and that the hypotensive effect of the drug is proportional to the level of plasma diazoxide achieved.[99]

The drug is usually given intravenously as a 300-mg bolus injection to reduce the blood pressure acutely. This regimen is safe for most patients; however, excessive hypotension has been described with this dosage.[100] This is especially true in patients in whom there is sympathetic blockage because there is no reflex increase of cardiac output to compensate for the hypotension. Adequate hypotensive responses can be obtained by using smaller doses repeatedly until the desired effect is achieved. The drug should not be given to patients with ischemic heart disease, because the reflex tachycardia can precipitate myocardial infarction.

Diazoxide, like other vasodilators, is associated with salt and water retention; thus, a diuretic is frequently given with diazoxide. In malignant hypertension the use of diuretics with diazoxide should not be used routinely because these patients frequently suffer from volume depletion. Moderate salt restriction should be sufficient to prevent excessive accumulation of salt and water in these patients.

Hypertrichosis and hyperuricemia are seen when the drug is used chronically. Hyperglycemia can occur with only a few days' use of the drug because of its potent inhibitory effect on insulin release.[101] Blood glucose levels should be monitored closely in patients with adult-onset diabetes when diazoxide is used because the drug can precipitate hyperosmolar coma.

Nitroprusside. Sodium nitroprusside is a very potent intravenous antihypertensive agent that

has acquired popularity in the past five years. The molecular structure of the drug has a ferrous center surrounded by five cyanide groups and a nitrosyl group. It is the nitrosyl group that is responsible for the drug effect on vascular smooth muscle.[102] Unlike the other peripheral vasodilators (diazoxide, hydralazine, minoxidil), nitroprusside has a significant dilatory effect on both the venules and arterioles, thus both preload and afterload are affected. Also, unlike the other vasodilators, the use of nitroprusside is not associated with a reflex increase in cardiac output.[103] The drug is very useful for hypertensive emergencies as well as for decreasing cardiac preload and afterload in patients with congestive cardiac failure. The usual dosage is 1 μg per kg of body weight per minute, but sometimes a 20-fold to 30-fold higher dosage is required to achieve a hypotensive effect. The advantage of nitroprusside is its very rapid action which allows for fine adjustment of blood pressure by titrating the infusion rate. The disadvantage of the drug is the close nursing supervision that is required because accidental speeding up of the intravenous infusion will result in severe hypotension. The drug is unstable when exposed to light; therefore, the infusion bottle should be wrapped in aluminum foil, and a fresh solution should be prepared every four hours.

Sodium nitroprusside is metabolized initially to cyanide and then to thiocyanate.[104] Acute cyanide intoxication has been reported with the use of sodium nitroprusside, but it occurs only if the dosage of the drug is above 15 μg per kg of body weight per minute.[105,106] Prolonged therapy with the drug results in thiocyanate accumulation especially if renal function is impaired. The usual symptoms of thiocyanate toxicity are confusion, slurred speech, weakness, muscle twitching and tinnitus, and may progress to stupor if the administration of the drug is not discontinued. If prolonged infusion of sodium nitroprusside is required, thiocyanate levels should be checked at least once a day; if the level is above 10 mg per dl, the infusion needs to be terminated. Overall, sodium nitroprusside is a safe and versatile drug that has significantly improved therapy for hypertensive emergencies.

Overall Approach to Treatment of Hypertension

One of the biggest problems in the treatment of hypertension is patient compliance. It would seem logical that improving compliance would improve the overall treatment of hypertension. Because all drugs have side effects, it is important to individually tailor therapy to minimize discomfort to each patient. However, the patient must take responsibility for his illness and realize that his life-style may have to be altered slightly if he is to live longer.

One basic principle that should apply to all drug therapy is that the less frequently a drug is taken, the more likely it is that the drug will be taken. Thus, a once-a-day regimen is better than twice daily, but twice a day is better than four times a day. Because almost all antihypertensive drugs can be given twice per day, compliance from this point of view should be good. Also, the fewer the drugs used to control blood pressure, the easier will be compliance. If blood pressure could be controlled using one drug once a day, overall compliance would be expected to improve.

Another major problem in treating hypertensive patients is that most of them are asymptomatic; however, annoying side effects develop after initiation of drug therapy. Unless patients are well educated about the consequences of hypertension, it is easy to understand why many do not continue to take their medication. Implementing some self-assessment of blood pressure control has been shown to be helpful in overall compliance.[107] If a patient were to record his own blood pressure two times a day, not only would the physician get a better idea of his patient's hypertensive control, but the patient also would have some concrete goals to work towards that he could assess each day. This form of self-assessment of control would be similar to that practiced by diabetic patients who check urine glucose levels.

Recommendations for specific drugs in treating hypertension are difficult to make unless the overall life-style and habits of each patient are evaluated individually. Obviously, if a patient makes his living as a bus driver, drugs like methyldopa and clonidine will be inappropriate because of central depressive effects. A patient who is athletically active may not do well taking high doses of propranolol because of the drug's ability to inhibit exercise-induced tachycardia. However, this same patient may find low doses of propranolol combined with a peripheral vasodilator to be a satisfactory regimen. In a patient with adult-onset diabetes this condition may be

made worse by thiazide diuretics because the drugs interfere with insulin release. Yet, propranolol may be effective in such a patient. On the other hand, an insulin-dependent diabetic patient may find the use of propranolol unacceptable because it interferes with the warning signs and symptoms of hypoglycemia. Patients with stable angina pectoris may find that peripheral vasodilators such as hydralazine increase the severity of the angina, and may actually precipitate a myocardial infarction even when used together with a beta-adrenergic blocking agent.

Cost is a consideration in treating a lifelong disease. The least expensive drug for the treatment of mild hypertension is a thiazide diuretic. If the hypertension is more severe, the addition of a peripheral vasodilator and a beta-adrenergic blocker will, in most cases, bring the blood pressure under control. The advantage in using peripheral vasodilators instead of sympathetic nervous system blocking agents such as guanethidine is that there is no orthostatic component involved in lowering blood pressure. In patients with arteriosclerotic heart disease, methyldopa or clonidine can be substituted for hydralazine to avoid the risk of reflex tachycardia and increased myocardial oxygen consumption.

Conclusion

Ideally, an antihypertensive regimen should be simple (one or two drugs, twice a day) and each patient should be made aware of possible side effects of the drugs before beginning therapy. Patients should actively participate in monitoring the control of their illness. And physicians should work with patients so that together they can control blood pressure with the fewest drug side effects.

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Leptospirosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. NAUGHTON:* *The topic of this conference is leptospirosis. It once was traditional at Medical Grand Rounds to have the patient in attendance during a case presentation. We will briefly return to this tradition in the case presented by Dr. Sandy Lawrence.*

DR. LAWRENCE:† This case presentation is unusual in that I was the patient. I had an illness several months ago, during the course of which I was admitted to hospital here twice. I was in my usual state of health until five days before the first admission. At that time I noted the development of malaise and anorexia, and then mild chilling throughout that first night. By the next morning, within 12 hours of onset of symptoms, I was feeling very ill. During that day a nonproductive cough and generalized myalgias developed. My temperature by then was 38.8°C (101.8°F) and remained higher than that for several days despite antipyretic treatment. On the third day of illness, classic migratory polyarthralgias of the large joints developed, specifically of the elbows, knees and ankles. On the fifth day, although I had been anorectic since the onset of symptoms, I had an episode of vomiting. I decided to visit the emergency room. While going through the paper work and then waiting to be examined I withdrew from the antipyretic drugs and underwent a shaking chill for about an hour. At that point, I felt and looked very sick and, therefore, was admitted. I had no rash, conjunctivitis, diarrhea, jaundice or headache.

I did have a fairly extensive history of exposure. Besides my work at San Francisco General Hospital as a resident, I had also done some traveling in the several months previous to my illness. I had been on vacation in Alaska three months before admission, and six weeks before onset of illness I had taken a brief trip to Okinawa and Malaysia. Perhaps the most significant exposure, however, occurred three weeks before admission when I had been camping in Oregon and swimming in a river.

On physical examination, I was febrile to 38.9°C (103°F); results of the examination were otherwise unremarkable. There were no skin lesions or adenopathy. Conjunctivae and fundi were normal. There were some palatal petechiae. The chest was clear, and heart sounds were normal. The liver percussed out to 9 cm, 1 cm below the right costal margin, but was not tender and there was no spleen palpable.

Significant laboratory data included an initial leukocyte count of 5,900 per cu mm. The differential was 89 percent polymorphonuclear leukocytes and no bands, 9 percent lymphocytes, none

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of which was atypical, and no eosinophils. The hematocrit was 46.5 percent, the blood urea nitrogen (BUN) was 40 mg per dl and the creatinine was 1.7 mg per dl. Analysis of the urine showed the following abnormalities: 3+ proteinuria, two to five leukocytes per high-power field, and two to five erythrocytes per high-power field. Results of liver function tests were also abnormal as follows: serum glutamic oxaloacetic transaminase (SGOT), 108 units per ml; serum glutamic pyruvic transaminase (SGPT), 124 units per ml, and alkaline phosphatase, 143 units per liter. Albumin was decreased to 3.1 grams per dl. Prothrombin time and total bilirubin were within normal range. An x-ray of the chest showed no abnormalities.

It appeared that I had a viral illness, though the course was not exactly consistent with hepatitis A or B, or with cytomegalovirus, infectious mononucleosis, or one of the enteroviruses. Three blood cultures as well as a urine culture were negative. I was rehydrated. I regained my appetite and was discharged home in two days. At home, I noticed that I was still febrile in the range of 38° to 39°C (100.4° to 102.2°F) when not taking antipyretic drugs. Then, on the third day after leaving the hospital, the worst headache of my life developed, accompanied by photophobia. Within 24 hours after the headache began, I noted some nuchal rigidity and I returned to the hospital.

On the second admission, my temperature was 37.7°C (99.9°F) and there were only two new findings on physical examination: I had mild conjunctival suffusion and minimal meningeal signs. Significant laboratory data included a leukocyte count of 5,700 per cu mm, with no bands or atypical lymphocytes. The hematocrit was 38.9 percent, and an analysis of the urine showed only trace proteinuria. Azotemia had resolved with a serum creatinine level of 1.1 mg per dl. However, on the tenth day of the illness, peak liver function test abnormalities were noted. The findings included the following: alkaline phosphatase, 163 units per liter; SGPT, 288 units per ml; SGOT, 182 units per ml, and lactic dehydrogenase (LDH), 232 units per ml. The level of bilirubin was still within normal limits, measuring 0.8 mg per dl. Results of a lumbar puncture showed an opening pressure of 190 mm of water; and levels of protein were 53 mg per dl and glucose, 46 mg per dl. Pleocytosis was present, with 17 erythrocytes per cu mm and 73 leukocytes per cu mm, 46 percent of which were polymorphonuclear. I received high-dose penicillin (20 million units a day) therapy intravenously for 48 hours until blood, urine and cerebrospinal fluid cultures were negative. I remained in hospital for another 24 hours and then refused a follow-up lumbar puncture and went home. The significant serologic findings included negative titers for *Mycoplasma,* toxoplasmosis, Q fever, infectious mononucleosis, VDRL and hepatitis B surface antigen. The indirect hemagglutination test for leptospirosis was initially negative, but four weeks after the onset of illness, it was positive at 1:400. Additional serologic tests will be discussed by Dr. Jacobs. The course of my illness was one of progressive resolution of symptoms. Liver function test results had returned to normal after about two weeks from onset. I was back at work a few days following that, but I did not feel completely well for another month.

DR. NAUGHTON: *I remember the discussion of Dr. Lawrence's case at our daily residents report. Dr. Alan Guerci, one of our chief residents, raised the possibility of leptospirosis on the first admission, but his suggestion was not met with a great deal of enthusiasm. When Dr. Lawrence was readmitted with the second phase of his illness the idea of leptospirosis gained considerable support and, as noted, subsequent serologic studies confirmed Dr. Guerci's initial diagnosis. This case will be discussed by Dr. Richard Jacobs.*

DR. JACOBS:* Leptospirosis can have variable clinical manifestations. The benign biphasic illness experienced by Dr. Lawrence is characteristic of anicteric leptospirosis, and is seen in approximately 90 percent of leptospiral infections. The initial description of this disease, however, was that of a much more severe illness. In 1886 the German physician Adolph Weil, in an attempt to separate the various causes of jaundice, described an illness characterized by jaundice, renal insufficiency, hypotension, confusion and hemorrhage that often resulted in death. It was not until some 30 years later, in 1915, that Inada isolated the causative agent, a spirochete, and called it *Spirochaeta icterohaemorrhagiae* in deference to the major clinical manifestations that Weil had described earlier.[1]

It is interesting, and somewhat surprising, that we have known about leptospirosis for more than 90 years. The clinical manifestations have been

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TABLE 1.—*Taxonomy of* Leptospira

Order	Spirochaetales	
Family	Treponemataceae	
Genus	*Leptospira*	
Species	*Leptospira interrogans*	
Complex	Biflexa, Interrogans	
Serogroups	Andamana	Hebdomadis*
	Australis	Icterohemorrhagiae*
	Autumnalis*	Javanica
	Ballum	Panama
	Bataviae	Pomona*
	Canicola*	Pyrogenes
	Celledoni	Sherman
	Cynopteri	Tarassovi
	Grippotyphosa*	

*Most common human pathogenic serogroups.

well described, and yet very little is known about the pathophysiology of this disease. I wish to give an overview of leptospirosis with emphasis on its epidemiology, clinical manifestations, diagnosis and therapy, and what little is known about its pathophysiology.

Taxonomy and Nomenclature

Leptospires belong to the order Spirochaetales. They are tightly coiled spirochetes that are 6 to 20 μ in length, and approximately 0.1 μ in diameter.[2] When viewed by dark-field examination they have a characteristic rotatory motion along their long axis,[3] and it has been postulated that this rotatory, boring motion is responsible for the tissue penetration of this organism. Like treponemes, which are also in the same family, leptospires do not stain with analine dyes, and thus will not be seen in preparations treated with Gram or Wright stain. They do, however, stain with silver, and if silver impregnation techniques are used these organisms are readily visible.[3]

The classification of leptospires is complex, and is important in understanding the serologic tests used in making the diagnosis (Table 1). The genus *Leptospira* contains only one species, *Leptospira interrogans*. This is divided into two complexes, the biflexa complex and the interrogans complex. Organisms of the biflexa complex are considered saphrophytic and, with rare exceptions, do not cause disease in humans. In contrast, organisms within the interrogans complex are parasitic and are responsible for disease in humans and in animals. At present, there are more than 150 antigenically distinct serotypes in the interrogans complex. Some of these serotypes share major antigenic determinants as disclosed by cross-agglutination tests, and these have been grouped together into serogroups.

Because the classification of leptospires is confusing, a comment about terminology is needed. The history of leptospirosis is such that initially distinct clinical syndromes of unknown cause were described in the literature, and only later were these syndromes proved to be due to infection with leptospires. Consequently, numerous descriptive phrases reflecting clinical syndromes have been used synonymously with leptospirosis. Perhaps the best example of this is Fort Bragg fever or pretibial fever. A benign, self-limited illness characterized by fever, splenomegaly and a pretibial rash was first described in army personnel at Fort Bragg, North Carolina in 1942.[4] About 40 cases were seen in the summer of 1942 and a similar number were observed during the following two years. It was not until 1952, ten years later, after 259 animal passages, that the causative agent was found to be a leptospire of the Autumnalis serogroup.[5] Similarly, other descriptive terms have appeared in the literature. "European swamp fever" in Poland, "mud fever" in Germany and "pea-pickers' disease" in the Far East have been used to describe similar illnesses that eventually were shown to be due to infections with leptospires of the Grippotyphosa serogroup.[6] Thus, several different terms have been used to describe a similar illness caused by organisms from the same serogroup. Furthermore, many early investigators felt that each serotype could produce only one specific clinical syndrome. It is known now that this is not the case. A given serotype can produce a wide spectrum of clinical illnesses and a given syndrome can be produced by several different serotypes. Accordingly, to avoid confusion descriptive terms should not be used and all leptospiral infections should be designated "leptospirosis," followed by the identification of the serotype if this is known (such as leptospirosis due to *L grippotyphosa* or leptospirosis due to *L icterohaemorrhagiae*).[7] The only exception to this is Weil disease. Because of its distinct clinical manifestations and the pivotal role it has played historically, the term is acceptable; but again, it should be followed by the name of the serotype when known.

Epidemiology

Leptospires are parasites of wild and domestic animals, and infection in humans is incidental and nonessential in the maintenance of these

organisms in nature. They are worldwide in distribution, and almost any animal can become infected. Of the wild animals, rodents are clearly the most important in transmitting disease to humans, and of domestic animals, dogs, cattle and swine are the most important. Infection in humans occurs in one of two ways: either a person comes into direct contact with infected animal tissue or he or she is exposed to soil or water that has been contaminated with leptospires. The natural reservoir for leptospires is the animal world, and following exposure, some animals become ill and die; others survive. Of those that survive some become permanent excreters of leptospires in their urine. Unlike the condition in humans, where leptospiuria is transient, in animals, leptospiuria can be chronic, sometimes persisting for the duration of the animal's life. Thus, if animals deposit leptospires in soil or water, and the appropriate conditions exist (the presence of moisture, temperature of about 25°C and a neutral or alkaline environment), the leptospires can replicate and persist for long periods of time. If a person comes into contact with the contaminated soil or water, he or she can become infected.

The epidemiology of leptospirosis has shown several interesting trends over the years. Initially, it was felt that humans could become infected only by direct contact with infected animals. Thus, leptospirosis was considered an occupational disease. Veterinarians, farmers, and workers in slaughterhouses who were exposed to infected cattle and swine, as well as sewer and dock workers who were exposed to infected rats, were considered at greatest risk for the development of the disease.[8] It became obvious, however, that during some recreational activities one also could become exposed to leptospires. Historically, the reasons for this extended incidence were that people were enjoying more leisure time and, simultaneously, farm lands and farm ponds were becoming available for recreational use. Several outbreaks of leptospirosis were described that could be traced to ponds that had been shared by animals and humans.[9-11] Animals that had been grazing would deposit leptospires from their urine into the soil and water. Later, persons using the ponds for recreational purposes became infected.

Dr. Lawrence had several possible exposures, including trips to Alaska and to Malaysia. The one most likely to be responsible for his illness, however, was the outing in Oregon. During that trip he was boating and swimming in a river that traversed farm land. When specifically questioned about the presence of animals, Dr. Lawrence recalled that numerous horses and cattle were grazing on the surrounding land. Most likely, some of those animals were excreters of leptospires in their urine and were responsible for contaminating the river.

Over the last several years the incidence of leptospirosis in persons without occupational exposure and who have never left the city has been rising,[12] and it is now accepted that leptospirosis is an urban and suburban disease. This aspect of the epidemiology of leptospirosis was described by Feigen and colleagues[13] who investigated an outbreak of leptospirosis in two families from an upper middle-class neighborhood in St. Louis. These investigators discovered that all of the rats isolated from the sewer system in the neighborhood were excreters of leptospires in their urine. In addition, at the time of the outbreak there had been increased rainfall and the soil was particularly alkaline, thus being very conducive to the growth and long-term survival of leptospires. They postulated that the family dogs had come into contact with the soil that had been contaminated by rats. Although the dogs had not become ill, they had become chronic excreters of leptospires and, subsequently, transmitted the disease to their owners. It is interesting that in this study both of the dogs that were examined had been vaccinated against leptospirosis. It is clear that if domestic animals are vaccinated, one can prevent disease in them. However, vaccination may not prevent the animals from becoming chronic excreters of leptospires and, thus, capable of transmitting disease to humans.

Some of the epidemiologic aspects of leptospirosis that have been mentioned here are emphasized in the Center for Disease Control's annual summary on leptospirosis for 1978.[12] During that year, 108 cases were reported and 51 percent were the result of avocational activities. A significant number of the occupationally related cases were the result of two epidemics, one in Florida and one in Oregon. For the preceding five years only 22 percent of the cases had been occupationally related, again emphasizing the shift in epidemiology and illustrating that leptospirosis is becoming an urban and suburban illness unrelated to occupation. There is a predilec-

tion for leptospirosis to occur in warm climates and during the warm months of the year. Most of the cases in 1978 occurred in the southern area of the United States. Similarly, the peak incidence of disease occurred in summer, from June to September. A fact that is poorly understood but consistently noted is that men are more likely to become infected than women. In 1978, 82 percent of cases were in males and only 18 percent in females. Finally, leptospirosis is primarily a disease of young adults. Some 37 percent of the cases occurred in persons between 20 and 29 years old; 75 percent of all cases in 1978 were in those younger than 39 years of age.

Clinical Manifestations

The clinical manifestations of leptospirosis are pleomorphic, and the severity of illness covers a wide spectrum. At one end is asymptomatic leptospirosis and at the other end is a severe illness characterized by jaundice, renal failure and hemorrhage, which is known as Weil disease. In between these two extremes is anicteric leptospirosis, a benign self-limited illness that rarely results in significant morbidity or mortality.

Asymptomatic Leptospirosis

A person can be exposed to leptospires, become infected with them and mount an immunologic response without ever experiencing a clinical illness, as indicated by results of serologic studies. Serologic evidence of previous leptospiral infection was found in 1.3 percent of an unselected hospital population.[14] In contrast, asymptomatic persons who work in high-risk occupations have a much higher incidence of positive serologic findings. Evidence for previous infection was found in 6.4 percent of 238 packinghouse workers,[14] 3.8 percent of dairy farmers and 2.6 percent of cattle ranchers.[15] These serologic studies leave little doubt that asymptomatic leptospirosis exists. Although unimportant clinically, it is important to realize that epidemiologically the incidence of leptospirosis is still not known. Any number that appears in the literature will be an underestimation of the true incidence because most statistics are based only on symptomatic cases.

Anicteric Leptospirosis

The most common form of the disease, and the one that Dr. Lawrence had, is anicteric leptospirosis. It occurs in 90 percent to 95 percent of symptomatic leptospiral infections.[7] Following the entrance of leptospires into the body through a break in the skin or through the mucous membranes, there is an incubation period of 5 to 20 days, the average being about 10 days.

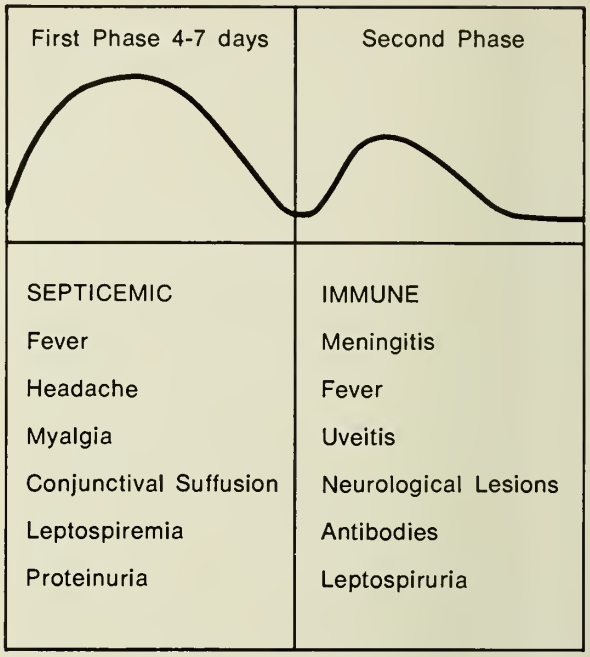

Figure 1.—The stages of leptospirosis. (Reproduced with permission from Edwards and Domm.[7])

The clinical manifestations of the ensuing illness have been well described by several authors.[6-8,13,16-18] Usually anicteric leptospirosis is a biphasic illness (Figure 1). The first phase of the disease is known as the septicemic or leptospiremic phase because leptospires can be isolated from the blood and cerebrospinal fluid. The second phase is known as the immune phase because the major clinical manifestations are thought to be the result of the body's immune response to infection. During this stage, leptospires can be isolated routinely from the urine.

The onset of the septicemic phase is usually abrupt, and has been described as a "brutal beginning."[7] Generally, patients are able to date the exact hour of the onset of their disease; occasionally, as occurred in Dr. Lawrence's case, there are two to three days of generalized malaise before the onset of more specific symptoms. Typically, the septicemic phase is ushered in by a rapidly rising temperature with chills, headache, severe myalgia and malaise. Thereafter, the patient continues to have high spiking fevers with chills, unrelenting headache, myalgia, abdominal

TABLE 2.—*Features of Anicteric Leptospirosis in First Phase*

Present in over 50% of patients
Headache
Fever
Chills
Myalgia
Gastrointestinal complaints
Anorexia
Nausea
Vomiting
Constipation/diarrhea
Conjunctival suffusion
Present in 25-50% of patients
Abdominal pain
Pulmonary manifestations
Cough
Hemorrhage
Rash
Retrobulbar pain
Arthralgia
Present in 5-25% of patients
Splenomegaly
Lymphadenopathy
Altered state of consciousness
Rarely present in patients
Acute arthritis
Parotitis
Epididymitis
Orchitis
Myocarditis
Pancreatitis

pain and various gastrointestinal complaints, usually including nausea and vomiting. These symptoms persist for four to seven days, following which there is defervescence and symptomatic improvement. This improvement correlates with the disappearance of leptospires from the blood and the appearance of specific antibodies in the serum. Following a latent period of one to three days, any or all of the signs and symptoms of the first phase may recur, although most characteristically, the patient experiences a recurrence of fever and the onset of aseptic meningitis.

In contrast to the nonspecific, monotonous and almost predictable presentation of the first stage of the disease, manifestations of the second stage are often variable, and several permutations can occur. Not everyone experiences a second phase of the disease. Some 10 percent to 15 percent of patients will simply have an acute febrile illness that also is characterized by headache and myalgias. Fever may or may not be present during the second phase; if it is present, it is usually of a lower amplitude and shorter duration than that seen in the first phase. Similarly, the latent period, usually lasting only one to three days, may be as long as seven to ten days. Meningitis is variable as well. It may or may not be present, and when present it may be very mild, lasting only one or two days or it can be severe, lasting several weeks.

A number of signs and symptoms in addition to those already mentioned can occur during the first phase (Table 2). Although Dr. Lawrence did not have a headache during the first few days of his illness it is almost always a symptom in the first stage of the disease, and it frequently is unresponsive to the use of routine analgesics. The cause of the headache is not clear. It is not due to increased intracranial pressure as there is no papilledema and the opening pressure on lumbar puncture is normal. Similarly it is not due to meningitis. Although leptospires can be isolated from the cerebrospinal fluid during the first stage, their presence does not elicit a cellular response; therefore, by definition, meningitis is not present. The headache usually lasts five to seven days and then disappears for a brief time. If it persists longer it will intensify, marking the onset of the aseptic meningitis that is characteristic of the second phase of the disease. Fevers and chills are also almost universally seen during the first phase. Most often fever is low grade, 37.8° to 38.3°C (100° to 101°F), but it can be as high as 40.6°C (105°F). Usually there is no distinctive pattern to the fever although on occasion spikes twice a day have been noted. Chills with frank rigor are common on the first day of illness and probably correspond to the initial leptospiremia. They may continue for several days early in the course, but shaking chills are almost never seen during the second phase.

Myalgias are not as common as headache, fever and chills, but they are one of the hallmarks of the disease. They may be generalized or occur locally in specific muscle groups, most commonly the calf, thigh and abdomen. Severe abdominal myalgia with fever can mimic the appearance of acute appendicitis, and surgical operations have been done on some patients. Myalgias are prominent early in the disease, but decrease in severity with time. They are less of a problem during the second stage.

The gastrointestinal symptoms are very common, occurring in as many as 90 percent of patients. They are nonspecific and the pathophysiology is poorly understood.

The ocular manifestation of the first phase of the illness is limited to conjunctival suffusion. It usually appears on the third or fourth day of ill-

ness and only lasts a few days, although it can persist for weeks. It is important to note that there is no chemosis or exudate; therefore, by strict criteria, there is not a true conjunctivitis. The clinical appearance has been likened to the condition of a person's eyes who has been swimming open-eyed in fresh water; this analogy is particularly helpful in emphasizing the hyperemia without exudate that is seen.

The other manifestations of the first phase of leptospirosis, listed in Table 2, occur much less frequently. Of particular interest is the rash. Ordinarily, the rash is evanescent, truncal in distribution and nonspecific. It can be macular, maculopapular, petechial or involve any combination of these. Several interesting variations of this rash have been described. Some patients have recurrent urticaria throughout the course of their disease. Symptoms of the illness first described in Fort Bragg, North Carolina, in 1942 (mentioned earlier), included—in addition to the usual manifestations of the septicemic phase—splenomegaly and a distinctive rash that occurred on about the fourth day of illness. The rash was erythematous, usually bilateral and limited to the pretibial area, although in a few cases it became generalized.[4] Finally, a very unusual form of skin eruption seen in children is a desquamative rash that occurs over the digits, often in association with digital vasculitis and gangrene.[19] The clinical appearance has been likened to that seen in the mucocutaneous lymph node syndrome or Kawasaki disease.

Findings during the immune phase of the disease include fever, meningitis (as well as various other neurologic manifestations), anterior uveitis and leptospiruria (Table 3). The hallmark of this phase is meningitis. Although meningitis is clinically present in only 50 percent of patients, one can detect abnormal findings in the cerebrospinal fluid in up to 86 percent of them.[7,20] Analysis of cerebrospinal fluid generally gives results that are similar to those associated with other causes of aseptic meningitis. Ordinarily, levels of protein are normal or slightly elevated and levels of glucose are normal as well. There is a mild pleocytosis, usually of less than 500 cells and with a predominance of mononuclear cells.[7,20] The pleocytosis usually disappears in 1 to 3 weeks, but can persist for as long as 60 to 80 days. The mechanism of the meningitis almost certainly involves an immune response. During the first phase of the disease, when leptospires are present in the cerebrospinal fluid, there is no cellular response; it is only when antibodies appear and leptospires disappear that the classic features of aseptic meningitis are seen.

TABLE 3.—*Features of Anicteric Leptospirosis During Second Phase*

Fever
Neurologic features
Meningitis
Encephalitis, myelitis, peripheral neuritis, cranial nerve palsies, paresis, Guillain-Barré syndrome
Anterior uveitis
Leptospiruria

There are animal models that support the concept of immune meningitis. If tuberculin is injected intrathecally into previously exposed animals, there is a cellular and pathologic response that is characteristic of aseptic meningitis, whereas similar injections into nontuberculous animals cause no reaction.[21] It is interesting that leptospirosis probably is a more significant cause of aseptic meningitis than previously appreciated. When serologic studies were done in patients with a diagnosis of aseptic meningitis, between 3 percent and 17 percent had evidence of a recent leptospiral infection.[22-24]

The other neurologic manifestations listed in Table 3 are only rarely seen in cases of leptospirosis. They probably occur on an immune basis and, in general, are self-limited, usually resolving without residua.

Anterior uveitis is an uncommon but interesting manifestation of leptospirosis. It usually occurs one to six months after the other signs and symptoms of the disease have disappeared, and like other second-phase manifestations, is probably mediated immunologically, although this is controversial. Clinically, it can present as uveitis, iridocyclitis or, uncommonly, chorioretinitis. It can be unilateral or bilateral and episodes are usually single and self-limited, although they can be multiple.[25] The mechanism of the uveitis has not been firmly established. On rare occasions leptospires have been isolated from the anterior chamber and a direct toxic effect has been postulated.[26] If this is the mechanism, it is unclear why the uveitis remains latent for so long and why it is so uncommon to isolate leptospires from the anterior chamber. The alternative explanation is that uveitis is an immune complex disease. In dogs previously infected with leptospires antibodies develop, and when leptospiral antigen is injected into the anterior chamber of these ani-

mals a clinical and pathologic response identical to that seen in human disease occurs. Similar injections into previously uninfected animals do not cause ocular inflammation.[27,28]

Leptospires can be isolated routinely from the urine during the second phase of the disease. Leptospiuria has no clinical significance—it is a transient state usually lasting one to three weeks and plays no role in the renal impairment seen in more severe forms of leptospirosis. Although theoretically the urine could serve as a route for person-to-person transmission of the disease, this phenomenon has never been observed.

Weil Disease

Weil disease is a more severe form of leptospirosis that has several distinct clinical features, including jaundice, renal insufficiency, hemorrhagic diathesis, hypotension and confusion. Although Weil disease is uncommon, accounting for only 5 percent to 10 percent of all leptospiral infections, it is responsible for all deaths due to this disease. Although initially it was felt that only the Icterohaemorrhagiae serotype caused this severe form of the disease, it is now recognized that other serotypes can also be responsible.

The onset of Weil syndrome is identical to that of milder forms of anicteric leptospirosis. The distinctive features of jaundice and renal insufficiency first make their appearance on the second or third day of illness, but generally do not reach a peak until the second week. Like anicteric leptospirosis, Weil syndrome tends to be a biphasic illness; however, because of the severity of the disease, this aspect is often obscured. Jaundice is the hallmark of this disease and extreme degrees of hyperbilirubinemia can be reached, sometimes as high as 60 to 80 mg per dl. The cause of jaundice is unclear. It does not appear to be due to biliary tract obstruction or to hemolysis; probably there is a subcellular defect in bilirubin metabolism and transport that accounts for this situation.

Mild degrees of renal impairment can be seen in anicteric leptospirosis, but severe forms of renal insufficiency with anuria and renal failure are limited to Weil syndrome. In some patients the renal insufficiency is due to prerenal factors; these respond very well to fluid administration.[29] Others, however, have features consistent with acute tubular necrosis[29]; histologically, the tubulointerstitial changes are identical to those seen in acute tubular necrosis due to other causes.[30,31] It is important to emphasize that the mortality in Weil syndrome is due to renal failure. With appropriate supportive techniques, renal failure is reversible and recovery of normal renal function is the rule.

Hemorrhage correlates with severity of disease. In anicteric leptospirosis hemorrhage is usually minor while in more severe forms of disease bleeding may be life-threatening and may manifest as hemoptysis, melena, hematuria or epistaxis.[7] A diffuse underlying vasculitis is felt to be responsible for the bleeding diathesis, although some patients have prolonged bleeding times, elevated prothrombin times and thrombocytopenia that may also play a role.[6,7]

Hypotension and shock are unique to Weil syndrome and are not seen in milder forms of the disease. Loss of blood, dehydration, carditis and fluid shifts from intravascular to extravascular sites have all been implicated.

Pathogenesis

It should be clear from the foregoing that a great deal is known about the clinical manifestations of leptospirosis, but very little is known about its pathophysiology. The most striking feature of this disease is the discrepancy between the pronounced organ dysfunction seen clinically and the minimal changes seen in these organs when examined microscopically. For example, in spite of severe hyperbilirubinemia and enzyme abnormalities, the liver may show only minimal degenerative and inflammatory changes when studied histopathologically. This discrepancy between function and histopathology has raised the possibility that perhaps the manifestations of leptospirosis are due to the elaboration of a toxin or toxins that act at a subcellular level.[6] Unfortunately, attempts to isolate such a toxin have been unsuccessful.

Methods described for the extraction of endotoxin from Gram-negative organisms have been applied to leptospires of the Icterohaemorrhagiae serotype. When the material obtained was subsequently injected into animals, no clinical or histopathological changes were seen.[32] These same investigators were able to show that extracts of liver from infected animals, when injected into other animals, were capable of producing hypothermia, diarrhea and a shock-like state leading to death. Histologically, changes similar to those seen in endotoxic shock were seen. Unfortunately, these findings have never been confirmed. The

anemia and jaundice seen in leptospirosis have been attributed to the elaboration of hemolysins. Indeed some serotypes do produce a hemolytic substance, but the clinical significance of this is unclear.[33,34] Pulmonary lesions can be seen in leptospirosis, but leptospires have never been isolated from the lung, again suggesting the possibility of a pulmonary toxin.[35] The list of proposed toxins is extensive[6]; but the fact remains that to date no substance produced by leptospires, which is capable of reproducing the clinical manifestations, has ever been isolated. Although it is appealing to postulate the existence of such a toxin, it must be concluded that if it exists, it must be extremely labile and difficult to isolate.

Diagnosis

Routine laboratory data are classically abnormal in leptospirosis. It is common to see minimal elevations in results of liver function tests in mild anicteric disease as well as in more severe forms of the illness, although pronounced hyperbilirubinemia is limited to Weil syndrome. Similarly, in about 70 percent of patients with mild disease abnormalities of the urinary sediment will be present and will be manifested as proteinuria, pyuria or hematuria.[36] Mild degrees of azotemia can also be seen, but oliguria and renal failure are limited to more severe forms of the disease. The leukocyte count is variable and severe anemia is seen only in Weil syndrome. A number of these laboratory abnormalities were noted in Dr. Lawrence's case. His liver function tests gave slightly elevated results, and he had proteinuria, microscopic hematuria, pyuria and slight azotemia, with a serum creatinine measurement of 1.7 mg per dl. In addition, his erythrocyte sedimentation rate was elevated, another abnormality frequently seen in leptospirosis. Obviously, these abnormal laboratory findings are nonspecific and when evaluated separately are not very helpful. However, when one sees a patient who has abnormal findings on analysis of urine and elevated liver function tests, in association with an acute febrile illness with conjunctival suffusion, the diagnosis of leptospirosis should be considered.

The definitive diagnosis of leptospirosis can be made in one of two ways: either by culturing the organism, or by showing serologic evidence of recent infection (Table 4). Contrary to popular belief, leptospires can be cultured easily in a laboratory, provided appropriate growth media are used and the appropriate specimen is submitted. Early in the course of the disease, leptospires are present in blood and cerebrospinal fluid, whereas during the immune phase of the disease they are found only in the urine. Thus, within the first week of illness, blood and cerebrospinal fluid specimens should be submitted for culture; during the second week, urine specimens should be cultured.

TABLE 4.—*Laboratory Diagnosis of Leptospirosis*

- Culture
  - Direct
    - Blood and CSF within 4-7 days of onset
    - Urine after 7th day of illness
  - Indirect
    - Animal inoculation
- Serologic findings
  - Species-specific tests
    - Macroscopic slide agglutination test (SA)
    - Microscopic agglutination test (MA)
  - Genus-specific tests
    - Hemagglutination test (HA)
    - Complement fixation test (CF)
    - Erythrocyte-sensitizing substance test (ESS)
    - Hemolytic test (HL)
    - Indirect immunofluorescent test (IF)
- Microscopic
  - Dark field
  - Immunofluorescent stain
  - Silver stain

CSF = cerebrospinal fluid

Because the concentration of leptospires in these fluids is often low, multiple specimens should be submitted. However, because of the presence of a growth inhibitor, only small amounts of blood and cerebrospinal fluid are cultured and urine is usually diluted before inoculation of the media.[2,6] At present, most laboratories use either Fletcher's semisolid medium or Stuart's liquid medium for the growth of leptospires.[2] Cultures should be incubated at 28° to 30°C in the dark. Because leptospires are slow growing, cultures should be kept for five to six weeks, although most become positive within the first two weeks.[2]

Animal inoculation is not used routinely for leptospiral isolation; however, it is a useful technique for obtaining purified cultures from those which have become contaminated with other microorganisms.

There are two general categories of serologic tests used in diagnosing leptospirosis, species specific and genus specific.[37] The species-specific tests allow one to assign a specific serotype to the probable infecting organism, whereas the genus-specific tests are less specific and only

TABLE 5.—*Summary of Serologic Tests Done in Case Presented*

Date	*Screening Test (indirect hemagglutination)*	*Species-Specific Test (microscopic agglutination)*
9/14	Negative	Negative
10/ 9	Positive	Positive Grippotyphosa 1:800 Djasiman 1:1600 Australis 1:100 Fort Bragg 1:50

TABLE 6.—*Diagnosing Leptospirosis*

Presumptive case of leptospirosis
- A patient with a clinical syndrome compatible with leptospirosis and having either:
  - Microscopic agglutination titer of 1:100 or greater *or* a positive macroscopic agglutination titer on a single serum specimen obtained after the onset of symptoms

    or
  - A stable microscopic agglutination titer of 1:100 or greater on two or more serum specimens obtained after the onset of symptoms

Confirmed case of leptospirosis
- A patient for whom any clinical specimen that is cultured for leptospirosis is positive
- A person with a compatible illness and either:
  - A seroconversion

    or
  - A four-fold or greater rise in microscopic agglutination titer between acute and convalescent serum specimens obtained two or more weeks apart and studied in the same laboratory

allow one to make a diagnosis of recent leptospiral infection without making a specific serotypic diagnosis. The microscopic agglutination test is the standard by which all other tests are measured. It employs live cultures of leptospires that are incubated with test serum. Because live leptospires are used in this test, it is a hazardous test to carry out; nevertheless, it is extremely sensitive and specific. As with the microscopic agglutination test the macroscopic slide agglutination test uses strains from each of the serogroups that occur in the United States. In the latter test, however, the antigen used has been killed. As a result, the test is safe to do, but is less sensitive and specific than the microscopic agglutination test. Both of these tests measure antibody that appears within the 6th to 12th day of illness, peaks in the third to fourth week, and may persist at low levels for years. The genus-specific tests, of which several exist (Table 4), take advantage of the fact that all leptospires share some antigens in common, and thus will cross-react with one another. In fact, the antigen that is used in most of these tests is derived from strains of the saphrocytic biflexa complex. These tests are nonspecific and not very sensitive, but are easily carried out and usually are done as screening tests in most laboratories.

A summary of the tests carried out on Dr. Lawrence's serum is shown in Table 5. The indirect hemagglutination test was used for screening. In the acute serum this test was negative, but subsequently became positive in the convalescent serum tested 3½ weeks later. Both of these sera were tested using the specific microscopic agglutination test. The acute serum was negative but the convalescent serum had high titers to two serotypes, Grippotyphosa and Djasiman. These data illustrate one of the difficulties of assigning a specific serotype to an infection solely on the basis of serologic data. Early in the course of the illness there can be cross-reacting antibodies present that make it impossible to tell exactly what the infecting serotype is. If the tests are repeated later, several months after the illness has resolved, antibodies to the cross-reacting serotype will probably have disappeared, leaving a high titer to only one serotype, which would be presumed to be the one responsible for infection. As can be seen in Table 6, the presence of a seroconversion constitutes definitive evidence of a leptospiral infection.

Several microscopic techniques have been advocated to confirm the diagnosis of leptospirosis (Table 4). These methods are nonspecific and fraught with technical difficulties, making them unreliable in diagnosing this disease.

Prognosis

The prognosis of leptospirosis depends on two things: the virulence of the organism and the age of the patient, and of these, the virulence of the organism is the more important. Virulence is reflected by the presence of jaundice. In uncomplicated anicteric leptospirosis death is virtually unknown. In more severe forms of the illness where renal failure and jaundice are present, death has been reported in up to 15 percent to 40 percent of the patients.[7,16,38] In these severe cases, renal failure is the cause of death. As noted above, renal failure is frequently secondary to acute tubular necrosis, a form of renal insufficiency that is often reversible. One might anticipate that with better supportive care and better dialysis techniques, the mortality would decrease. This, in fact, is the case: In 1978 the mortality from Weil

disease was only 5 percent compared with the 15 percent to 40 percent that had been described in the previous decade.[12]

Age is a less important factor in determining the outcome, but those patients who are more than 50 years old are more likely to have an unfavorable outcome than younger patients.[7,38]

Therapy

Several antibiotics have been shown to be effective against leptospires in vitro and in experimental animals. These include penicillin,[39] the tetracyclines,[40] erythromycin,[41] and cephalothin.[42] It is difficult, however, to apply these in vitro data to clinical situations. Most leptospiral infections are self-limited with a favorable prognosis and, thus, it would require a randomized and prospective controlled study with a large number of patients to discern any effect of antimicrobial therapy on this benign disease. To date there have been only three such studies. Two of them have shown no effect of antimicrobial therapy on the course of the illness,[43,44] and one has suggested that perhaps the early institution of penicillin therapy may prevent some of the complications of the disease, such as hemorrhage, jaundice, renal insufficiency and meningitis.[45]

Most infectious disease experts would agree that penicillin or tetracycline should be given if the diagnosis is suspected within the first 48 hours. Pathophysiologically it is at this time that leptospires are present in blood and invading tissue, and one might anticipate that treatment would be beneficial. On the other hand, if a patient has already entered the immune phase of the disease and has meningitis, renal failure or jaundice, antimicrobial therapy would not be expected to play a major role in determining outcome, and therefore would not be indicated.

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EDITORIALS

Topic A

THIS issue of THE WESTERN JOURNAL OF MEDICINE contains an impressive assemblage of informed views and statements on various aspects of "Topic A" in the health care field, which, of course, is how best to control or contain the ever rising costs of medical and other health care services. Each author is distinguished, and has more than average knowledge and experience with health care costs and what is being done about them on the national scene. The editors of *WJM* are grateful to each of them for taking the time and trouble to contribute to this special issue.

One thread that seems to run through many of the statements is that the health care enterprise of this nation (and with it the now troublesome escalation of health care costs) has developed or evolved in response to what the public has asked and expected of it, and that there is no reason even now to expect that this will change. In fact there already is evidence that effective steps are being taken within the enterprise to begin to respond to the need to control costs.

The record shows that shortly after World War II an enormous effort to develop medical science and technology was put in place in response to public demand and with public support. This was and continues to be fantastically productive. Then, in response to public demand for more access for more people to more health care services, and again with substantial public support, the health care enterprise constructed more facilities, produced more technology and trained many more physicians and other health professionals. The government also established costly programs of entitlement to medical and health care services for the elderly and needy which have not always been adequately funded. These too have been largely carried out by the health care enterprise in the private sector, which to some extent has had to subsidize them. Now, and again in response to a more recent public demand, the health care enterprise is focusing increasing attention on costs and how they can be controlled without sacrificing quality (which includes technology) or access (which includes governmental support of care for the aged and needy).

The record is one of responsibility and responsiveness by the health care enterprise. It augurs well for the American way of doing things. But, as Derzon says in his paper, what is now needed is less confrontation and more genuine collaboration between government and the highly developed and unique enterprise that provides health care services for the people of this nation, and does it rather well. Confrontation is seldom productive and always costly and the record shows this too.

—MSMW

Treatment of Hypertension: Empirical Versus Rational

GERBER, FREED AND NIES elsewhere in this issue have provided the reader of THE WESTERN JOURNAL OF MEDICINE with a scholarly review of the use of antihypertensive agents currently available for the management of high blood pressure. It is a concise distillation, giving us the essence of the theoretical basis for drug choice. Most of the information will be useful to those of us treating hypertensive patients—its primary value being a handy reference for information on mechanisms of action, side effects, toxicity and dosage schedule for all the principal agents and their alternatives.

However, the article will not serve as a practical guide for managing the vast majority of hypertensive patients who respond to either a diuretic alone or a diuretic in combination with one of several available antiadrenergic agents. In this sense, it cannot be equated with the recent, immensely practical and brief article by Feigenbaum[1] on the selection of step 2 drugs. Gerber and co-workers fail to recognize the enormously successful empirical approach known as stepped care, advocated by the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure.[2] Rather, they advance the concept of individual choice of drug or drugs for *each* patient, the rational approach. While this has enormous intellectual appeal, from a public health point of view it has never resulted in large numbers of patients in whom hypertension is

under effective control. Indeed, only since the National High Blood Pressure Education Program began its vigorous advocacy of an empirical approach has the proportion of hypertensive persons whose conditions are under control risen significantly. Associated with this has been a dramatic fall in deaths resulting from cardiovascular disease in general and strokes in particular.

The introduction of the topic of drug therapy, while accurate and concise, is much less complete than the review of drugs that follows, and is not the primary basis for commending the article. Briefly described are the nature and magnitude of the problem of hypertension in the United States, the arbitrariness of the pressure levels used to define it and, quite appropriately, the inappropriateness of extensive screening and workup to exclude secondary causes. The percentage of patients in the community (in contradistinction to those referred to medical centers), having other than primary hypertension, is even lower than the 5 percent estimated by the authors.[3]

A serious omission from the review of Gerber and co-workers, is the role of sodium intake and weight control in the management of hypertension. Medical treatment is equated solely with the use of drugs. Not only will most patients defined as hypertensive by the authors benefit from weight and sodium limitations in conjunction with drug therapy, in some there will be response to such nonpharmacologic measures alone.

The authors' statement that the usual dose of reserpine is 0.25 mg, while true, is ambiguous. It fails to make clear that it is also the maximum dose and that many patients are managed well with 0.1 or 0.125 mg in combination with a diuretic. In general, the authors unjustifiably relegate reserpine to an inferior role. Double-blind studies indicate no more side effects than with other step 2 drugs,[1] and on the basis of efficacy, convenience of dosage and lower cost, reserpine is considered by some to be the drug of choice.[1,4-7]

The principles espoused in the section entitled Overall Approach to Treatment of Hypertension are sound and need to be widely applied. And the importance of facilitating patient adherence to the prescribed regimen through minimizing the number and frequency of the medications and through involving the patients in an active and responsible way in their management deserves special emphasis. Self-measurement of blood pressures at home is a useful way to achieve this involvement, but measurements twice a day are seldom necessary once control is achieved.

Much progress has been made in our ability to control high blood pressure. This has not resulted from any breakthrough in new drugs or understanding of basic mechanisms. Rather, it is a consequence of the wider application of existing principles, information and drugs via strategies that improve compliance of physicians and patients alike. Gerber and colleagues, in reviewing the pharmacology of antihypertensive agents have given us a concise and valuable information resource. Its value in practice, however, will be realized by combining it with the stepped-care approach that has as its cornerstone the principle of using the fewest number and doses of drugs.

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An Idea Whose Time Is Here?

In this issue, Dr. Chris Holmes makes a plea for more attention to preventive medicine and more support for it within the medical profession and elsewhere. This is an appropriate commentary to include in this special issue of *WJM*, which is particularly focused on controlling the costs of health care. There are many who are convinced that if prevention can be carried to its ultimate, the costs of care will be commensurately reduced. There are others who question whether this would actually ever happen. They note that prevention itself costs something, and preventing one morbidity may leave the way open

for further and perhaps, in the end, more costly sickness. Be this as it may, prevention of illness, injury and emotional disturbance is clearly desirable. When it is successful, morbidity is avoided, mortality may be delayed and the quality of life of persons and communities is enhanced.

But, as Holmes points out, prevention is not always easy to sell as a segment of medicine which should receive a fair share of professional interest and public support. Perhaps those interested in advancing preventive medicine should begin to define its dimensions more clearly because at the moment, as is true for medicine itself, these dimensions seem too general and almost all-inclusive. However, those who espouse preventive medicine and seek support for it also have a special problem. By definition whatever is prevented never happens, and therefore cannot be measured in dollars or anything else. It would seem that more attention might be given to this and ways should be sought to measure the cost-effectiveness of prevention. For instance, poliomyelitis has been prevented. Would it now be possible to extrapolate the preimmunization incidence of poliomyelitis into what would have been the annual cost of the care of the projected victims in 1980 dollars? These would have been the health care costs in 1980 for this condition had not the disease been prevented. Such an approach to estimating the "prevented" costs might help to generate the interest in and support for preventive medicine which Holmes seeks.

But this writer cannot help wondering, when all is said and done, whether we really want to prevent everything. Some things, yes; but do we really mean all risk of illness, injury or emotional stress? Where will be the romance in living if there are no risks? This is especially true where human nature and human behavior are involved. People like to take risks. In a sense, the opportunity to take a chance is what life is all about, especially in a free society.

—MSMW

Complications of Anticoagulant Therapy

THE CASE REPORT on anticoagulant-induced bleeding of ovarian origin in this issue prompted this editorial. Students of anticoagulant therapy recognize the ovary as a well-known source of intraperitoneal bleeding.[1] In fact, 300 cases of intraperitoneal bleeding of ovarian origin were reported by 1937—before the era of anticoagulant therapy.[2] However, one reason for the low incidence of anticoagulant-induced ovarian hemorrhaging is that it occurs mainly in ovulating, menstruating women from a corpus luteum in the vascular premenstrual phase. Furthermore, anticoagulant therapy usually is prescribed for disorders that occur in nonovulating women, such as thrombophlebitis during pregnancy or puerperium and coronary artery disease following menopause.

There are many well-described bleeding syndromes associated with anticoagulant therapy that often simulate those of patients with congenital hemophilia. The occurrence of compression neuropathy is well known, particularly after percutaneous needle puncture of the brachial or femoral artery. Such complications underscore the need for obtaining arterial blood specimens from the radial artery, where manual pressure can be applied firmly after the puncture, in patients taking anticoagulant drugs.[3] Spontaneous retroperitoneal hemorrhage often appears as an acute femoral neuropathy because the extravasated blood passes underneath the tight fascia of the iliac fossa.[4] Anticoagulant-induced hemopericardium with tamponade can occur even in the absence of myocardial infarction or pericarditis, or after a cardiac surgical operation.[5] Intrarenal hematoma, adrenal hemorrhage, and even a hematoma within the abdominal rectus sheath[6] can occur during anticoagulant therapy. Often, the first symptom is acute abdominal pain, as it was in the case reported by Dr. Honoré.

The most serious bleeding syndromes during anticoagulant therapy are those of the central nervous system and the gastrointestinal tract. Gastrointestinal bleeding is often associated with intramural hematomas of the small intestine that have distinctive radiographic patterns.[7] These hematomas usually resolve with conservative management, and surgical extirpation of the hemorrhagic segment is contraindicated. Intracranial hemorrhage has been reported in more than 100 patients, most of whom died.[8] Spinal epidural hematomas also occur, which can be painless. A lumbar puncture may produce paraplegia, even when carried out shortly before the administration of anticoagulant drugs.[9]

The use of an orally given anticoagulant drug during pregnancy is dangerous because, unlike the

large and highly charged molecule of heparin, the small uncharged molecules of the drug equilibrate across the placenta into the fetal circulation. Thus, anticoagulant medication given orally to the mother in the first trimester can act as an abortifacient and cause fetal wastage, or as a teratogen, causing congenital anomalies such as skeletal enchondromatosis in the newborn.[10] These drugs administered in the third trimester can cause stillbirths as well as central nervous system damage secondary to the fetal intracranial bleeding that is frequently associated with the forces of labor. Whenever possible, heparin should be the only anticoagulant drug given to pregnant patients. Finally, anticoagulant-induced necrosis of the skin and of subcutaneous tissues, unrelated to the hypoprothrombinemic effect, has been reported in more than 150 patients, especially in obese women. It affects the fatty tissue of the breasts, buttocks, thighs and abdomen. The necrosis is caused by hemorrhagic infarctions associated with necrotizing arteritis and venous thrombosis, which are induced somehow by the orally given anticoagulant drug. These complications generally occur during the first two weeks of therapy.[11]

How can these hemorrhagic complications of anticoagulant therapy be avoided? Because bleeding usually results from an extension of the pharmacologic effect of these drugs, both physicians and, especially, patients must avoid all possible factors that can augment their hypoprothrombinemic effect. The three cornerstones of safe anticoagulant therapy are a carefully selected, well-informed, cooperative *patient* who is closely supervised by an experienced *physician* who is aided by suitable *laboratory* facilities for the accurate control of therapy.

Long-term anticoagulant therapy of a patient who is not in the hospital is hazardous unless the patient (or someone residing with him or her) is capable of taking responsibility for the therapy, has sufficient literacy in the mutual language of physician and patient and the visual acuity to read instructions, is intelligent enough to understand the serious nature of the therapy and the need for close control and supervision, and has shown consistency in keeping appointments.[12] Initially, the patient must be thoroughly examined by the physician to detect bleeding or any potentially hemorrhagic lesions and to identify absolute and relative medical contraindications to anticoagulant therapy. The physician must assess the risk of intracranial hemorrhaging in hypertensive patients and must screen all patients for potential sources of gastrointestinal bleeding.[13] Although the complicated details of laboratory control of anticoagulant therapy are beyond the scope of this editorial, the thorough report that was just published by an international panel of experts[14] should be consulted by all physicians who prescribe orally administered anticoagulant drugs.

Administration of anticoagulants on a long-term basis is a highly specialized form of treatment, and clinics devoted solely to these patients have been established. The highest therapeutic efficacy and lowest hemorrhagic toxicity of these drugs have been achieved in small European countries, such as Norway and Holland, where specialized centers have been established by physicians expert both in the clinical management and the laboratory control of this therapy. Risk factors for hemorrhagic complications during long-term therapy include poor supervision of the patient, use of orally administered anticoagulant drugs despite medical contraindications, poor laboratory control of the drug dosage, administration of large initial doses or a dosage that is too intense for the patient, concomitant administration of drugs, such as acetylsalicylic acid or barbiturates that interact with anticoagulant drugs given orally, and anticoagulant treatment of elderly or pregnant patients or patients with disorders of the gastrointestinal, gynecologic and genitourinary systems.[15]

Most of the bleeding episodes occur during the first two months or after three years of therapy. Therefore, the patient should be examined weekly in the clinic or office during the first few weeks for (1) detection of bleeding, (2) stabilization of drug dosage by monitoring the one-stage prothrombin times and (3) review of the patient's understanding and management of his or her own treatment. Physicians who are experienced in administering anticoagulant therapy provide their patients with detailed verbal and written instructions that (1) explain the danger signs of bleeding and symptoms of recurrent thromboembolic disease, (2) note the times to contact the physician, (3) warn the patient about relying on memory for the size and frequency of the drug dose, (4) urge the use of a calendar or diary for recording the amount of drug actually taken and (5) remind the patient to either carry on his or her person a wallet card or to wear a Medic-Alert bracelet or "dog-tag" necklace to alert medical

personnel in an emergency. Experienced physicians also give a supply of vitamin K_1 tablets to their patients for emergency use. Yet despite this detailed care, *bleeding often occurs even when the prothrombin time is within the expected therapeutic range,*[12] as happened in Dr. Honoré's patient. It is this aspect above all—the near-fatal bleeding when the patient's prothrombin time was only twice the control value—that gives such heuristic value to the case report in this issue.

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CASE REPORTS

Refer to: Luce JM, Huseby JS, Marini JJ: Bilateral diaphragmatic paralysis as a cause of respiratory failure. West J Med 132:456-460, May 1980

Bilateral Diaphragmatic Paralysis as a Cause of Respiratory Failure

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BILATERIAL DIAPHRAGMATIC PARALYSIS (BDP) has become an uncommon cause of respiratory failure since the decline of poliomyelitis and diphtheritic polyneuropathy. Therefore, physicians may overlook BDP and attribute its effects to other conditions. The case presented here underscores the need to consider BDP in the differential diagnosis of respiratory failure, and serves as a focus for discussion of the pathophysiology, evaluation and treatment of this disorder.

Report of a Case

A 17-year-old girl was well until March 1978, when her first full-term infant was delivered by cesarean section. Transient hypertension and generalized seizures occurred hours after delivery. These symptoms were attributed to eclampsia, and the patient was given phenytoin and phenobarbital. Over the next few weeks, the girl noted morning headaches, blurred vision and orthopnea. She then began to awaken at night with the sensation that she could not take a deep breath and the fear that if she fell back to sleep she would forget to breathe.

This fear became so intense that in May the patient could not sleep for two days. She finally took a 30-mg tablet of phenobarbital and fell asleep; however, she could not be awakened. She regained consciousness only after mechanical ventilation was instituted at a nearby hospital.

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ABBREVIATIONS USED IN TEXT

ABG = arterial blood gases
BDP = bilateral diaphragmatic paralysis
Pa_{CO_2} = arterial carbon dioxide tension
Pa_{O_2} = arterial oxygen tension
P_{ab} = abdominal pressure
P_{di} = transdiaphragmatic pressure
P_{pl} = pleural pressure
V_E = minute ventilation
V_T = tidal volume

At this time, the patient's history and physical examination showed no abnormalities. Findings of a complete blood count, study of electrolytes, toxicologic screen, lumbar puncture, tests for heavy metals, thyroid function tests, an x-ray study of the chest, electrocardiogram, porphyrin screen, determination of cortisol level, edrophonium chloride (Tensilon) test, electroencephalogram and computerized axial tomography of the head were all unremarkable. Arterial blood gases (ABG's) measured while mechanical ventilation was not being used and the patient was breathing room air were pH 7.32, arterial carbon dioxide tension (Pa_{CO_2}) 85 torr and arterial oxygen tension (Pa_{O_2}) 27 torr.

The patient's ABG measurements remained abnormal during the daytime, but she could breathe spontaneously off the ventilator and was able to carry out some normal activities. However, respiratory acidosis, hypercapnea and hypoxia worsened during sleep, and nocturnal mechanical ventilation, provided through a tracheostomy, was required. Use of a volume ventilator was continued at night while weaning was attempted with intermittent mandatory ventilation (IMV). On every occasion when the IMV rate was decreased, the patient's minute ventilation (V_E) did not increase and she awakened in panic. She eventually refused to sleep in any but the controlled ventilation mode.

During this period the patient ate poorly, and her weight fell from 90 to 66 pounds. She also stopped menstruating and appeared depressed. This prompted consultation from a psychiatrist, who suggested that the patient's weaning difficulties might be related to unwillingness to leave the hospital and assume her new maternal responsibilities. In August the patient was transferred to

our facility with the combined diagnoses of anorexia nervosa and primary alveolar hypoventilation.

At this time the results of physical examination were remarkable for a diminutive body habitus in the absence of weakness or other neuromuscular abnormalities. Her breathing pattern was characterized by rapid, shallow respirations and the use of intercostal and sternomastoid muscles. Paradoxical inward motion of the abdomen during inspiration was noted in the supine but not the upright position.

Laboratory findings were within normal limits except for an elevated level of creatinine phosphokinase (CPK); room air ABG measurements were pH 7.34, Pa_{CO_2} 48 torr and Pa_{O_2} 70 torr. The ABG's worsened in the supine position to pH 7.31, Pa_{CO_2} 56 torr, and Pa_{O_2} 58 torr. With this change of position, her tidal volume (V_T) fell from 260 ml to 195 ml, her respiratory rate rose from 25 to 28 per minute and her V_E fell from 6.5 to 5.4 liters. Upright pulmonary function tests (Table 1) showed moderate restriction, a substantially low vital capacity and the absence of airflow obstruction.

At fluoroscopy, diaphragmatic movement could not be seen during quiet breathing, sniff maneuvers and transcutaneous phrenic nerve stimulation. The diagnosis of bilateral diaphragmatic paralysis was confirmed by transdiaphragmatic pressure recordings, which showed negative pressure in both the thorax and abdomen during deep inspiration. Conduction velocities were not measurable in the phrenic nerve, although they were within normal ranges elsewhere. Electromyography (EMG) with both surface and needle electrodes showed positive waves and fibrillations suggestive of a neuropathic process in the diaphragm and, to a lesser extent, in the deltoid, rectus abdominus and intercostal muscles. Results of a right deltoid muscle biopsy were nondiagnostic.

A therapeutic trial of 40 mg per day of prednisone was initiated because of the patient's elevated levels of CPK; however, her diaphragmatic dysfunction persisted after the CPK measurement returned to within normal limits. She then assessed a variety of ventilating devices but could not overcome her dependence on a pressure-limited ventilator for sleeping at night. The patient was trained in chest physiotherapy and ventilator maintenance and left the hospital in November 1978. Aside from a single episode of bacterial pneumonia, which was treated with antibiotics given orally, she has remained well.

Discussion

In their recent review, Derenne and colleagues[1] noted that the diaphragm carries out all inspiratory work during quiet breathing in normal persons. The fibers of the diaphragm pass from rib to rib and are directed upward and parallel to the rib cage at the end of tidal exhalation. Because of this relationship, diaphragmatic contraction displaces the rib cage outward and upward as well as pushing down on the abdominal viscera. Normally, pleural pressure (P_{pl}) becomes more negative and abdominal pressure (P_{ab}) becomes more positive during inspiration, so that the abdomen moves outward and a transdiaphragmatic pressure (P_{di}) gradient is developed.

Diaphragmatic Paralysis

When the diaphragm is paralyzed, negative P_{pl} must be generated entirely by the intercostal and accessory respiratory muscles. This action not only expands the lung but also sucks the diaphragm into the thorax. The upward movement of the diaphragm results in a reduction of both P_{pl} and P_{ab}, so that the abdomen moves inward and a significant P_{di} is not generated. In addition, by opposing lung expansion, the upward movement of the diaphragm imposes an additional stress on the intercostal and accessory muscles.

TABLE 1.—*Pulmonary Function Tests in the Upright Position*

Test	*Predicted*	*Observed*	*Percent of Predicted*
Vital capacity (liters)	2.14	0.63	29
Forced expiratory volume in one second (liters)	1.86	0.63	34
Forced expiratory volume in one second (liters)/ vital capacity (liters) × 100	86	100	
Residual volume (liters)	1.49	1.88	126
Total lung capacity (liters)	3.63	2.53	70
Residual volume (liters)/total lung capacity (liters) × 100	41	74	
Functional residual capacity (liters)	1.91	2.07	109

In patients with BDP, paradoxical inward abdominal movement occurs throughout the respiratory cycle when they are in the supine position. However, in the upright position this paradoxical motion may occur only in late inspiration, according to Kreitzer and colleagues.[2] This happens because abdominal muscle contraction during expiration displaces the diaphragm upward. The subsequent relaxation of abdominal muscles at the onset of inspiration permits passive descent of the diaphragm and outward movement of the abdominal wall until contraction of the intercostal and accessory respiratory muscles in mid-inspiration causes diaphragmatic displacement upward once again.

The finding of paradoxical abdominal motion should prompt investigation of the effects of BDP on the patient's arterial blood gases and pulmonary function. BDP decreases total lung capacity, increases residual volume, and severely limits tidal volume and vital capacity, especially in the supine position. Because of a limited ability to augment V_T, patients often must increase respiratory rate to maintain alveolar ventilation. Those patients who hypoventilate may do so in part because they lack intact intercostal and accessory respiratory muscles. However, both McCredie and associates[3] and Newsom-Davis and colleagues[4] state that the degree of hypoventilation in a given patient with BDP depends not only on the extent of neuromuscular impairment, but also on the presence of wakefulness as a ventilatory stimulus and the preexistent or acquired blunting of respiratory drives.

Although BDP may be suspected if movement of the diaphragm is not shown on fluoroscopy, this procedure is associated with false-positive and false-negative results according to Newsom-Davis and colleagues.[4] Lourenco and Mueller[5] have advocated the use of diaphragmatic electromyography in the evaluation of diaphragmatic dysfunction, and Eldridge[6] has outlined methods for assessing electrical activity in the phrenic nerve. However, these techniques are neither well standardized nor generally available. Thus, Newsom-Davis and associates[4] believe that transdiaphragmatic pressure recording is the most reliable way to diagnose BDP. This technique involves the passage of esophageal and gastric balloons to measure P_{pl}, P_{ab} and the P_{di} gradient, as first described by Agostini.[7] The P_{di} gradient during deep inspiration should be 25 cm of water or greater in healthy subjects, whereas in patients with diaphragmatic paralysis it measures less than 5 cm of water. Although quantitation may be useful when diagnosing a patient's condition, BDP can be determined, as it was in our patient, by merely showing an absence of change in the polarity of pressure swings as a single balloon is withdrawn from the stomach to the esophagus.

Once BDP is confirmed, selected studies may help determine its cause. For example, phrenic nerve stimulation, as described by Newsom-Davis,[8] should show whether the diaphragm can respond to most types of therapeutic pacing. The absence of movement does not differentiate nerve from muscle dysfunction or define their severity, however. As a result, EMG, nerve potential determinations and a diaphragmatic biopsy may be necessary to determine the cause of the problem. It is of note that despite extensive investigation of our patient's disorder, the cause remains unknown.

Types of Treatment

Although some patients may only be compromised minimally by BDP, in others—those with generalized neuromuscular disease—long-term mechanical ventilation may be needed. Positive-pressure ventilators are familiar to most health professionals and lack the stigma of permanent disability or helplessness which many patients associate with negative-pressure body ventilators. Nevertheless, negative-pressure tanks are reliable and do not require permanent tracheostomy. In addition, Rochester and colleagues[9] have shown that body ventilators decrease the work of all the respiratory muscles and provide relief of dyspnea independently of changes in Pa_{CO_2}.

Several other devices are available for patients with BDP in whom continuous mechanical ventilation is not required. These include the rocking bed, the chest cuirass and the pneumobelt. The rocking bed stimulates diaphragmatic activity by imparting motion to the abdominal contents in time with the respiratory cycle; it does not require airway access or a ventilator, and is the simplest way of providing respiratory support if its seesaw movements can be tolerated. Our patient could not tolerate these movements and headaches developed while the rocking bed was being used.

The chest cuirass, a negative-pressure ventilator which is affixed to the front of the chest rather than covering the entire body, can be powered by a small battery-driven compressor unit no

larger than an overnight case, and may be effective if it fits the chest. Powner and colleagues[10] recently described bedside construction of a custom cuirass for a patient with kyphoscoliosis that conformed better than commercial models to their patient's deformity.

The positive-pressure pneumobelt intermittently compresses the abdomen and pushes the diaphragm into the thorax. The pneumobelt may be powered by the same portable compressor as the chest cuirass and is so compact that it may be worn under clothing. However, it is effective only when used in the upright position, and many patients find its squeezing action uncomfortable. Our patient tolerated the pneumobelt for short periods and now uses it to nap.

Another possible form of ventilatory support is bilateral phrenic nerve pacing or so-called electrophrenic respiration. This technique, as described by Glenn and colleagues,[11] uses an external frequency transmitter to activate receivers affixed to or overlying the phrenic nerves in the neck. Johnson and Eiseman[12] have implanted pacing electrodes directly into the diaphragm, and Daggett and associates[13] have used intracaval electrophrenic stimulation. The nerves generally are stimulated alternately for 12-hour periods to avoid nerve fatigue; stimulation of a single nerve provides ventilation adequate to maintain normal ABG measurements.

Electrophrenic respiration was used first by Sarnoff and colleagues[14] in treating respiratory failure due to bulbar poliomyelitis. Since then Glenn and associates[15,16] have applied the technique to patients with cervical cord injury and primary hypoventilation. Glenn and other coworkers[17] also have used diaphragm-pacing to improve ventilation at night in a patient with severe chronic obstructive pulmonary disease. Electrophrenic respiration may be applicable to many patients with BDP, and our patient in particular appeared to be an ideal candidate for nocturnal diaphragm-pacing. However, her phrenic nerves did not transmit electrical impulses when stimulated in the neck, and she was unwilling to undergo experimental implantation of pacing wires in the diaphragm.

The prognosis for patients with BDP is uncertain and depends on the cause of the disorder. Spitzer and colleagues[18] have described the spontaneous remission of respiratory failure 15 months after the onset of orthopnea in a middle-aged man with postinfectious phrenic neuritis. By contrast, Schmalstieg and associates[19] reported the case of 20-year-old woman in whom respiratory failure developed due to BDP late in her pregnancy. She died four months later of a fulminant polyneuropathy. Although the cause of her BDP remains unknown, our patient recently noted voluntary diaphragmatic movements; and for the first time there has been positive P_{ab} on transdiaphragmatic pressure recording. This may indicate a return in phrenic nerve function.

Conclusion

We wish to emphasize that although BDP is a rare cause of respiratory failure it should be considered in patients in whom this failure is not readily explainable. Bilateral diaphragmatic paralysis should be suspected particularly if paradoxical inward motion of the diaphragm occurs during inspiration. The diagnosis of BDP is suggested by fluoroscopy and confirmed by transdiaphragmatic pressure recordings. Although the cause of BDP may be obscure in some cases, the respiratory failure it causes can be treated by a variety of devices, and spontaneous remission has been reported.

We have presented our case report to point out the diagnostic evaluation needed to determine BDP as the cause of respiratory failure, and to discuss various types of treatment available to assist ventilation.

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Refer to: Honoré LH: Ovarian hemorrhage: A complication of long-term anticoagulant therapy. West J Med 132:460-461, May 1980

Ovarian Hemorrhage: A Complication of Long-Term Anticoagulant Therapy

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OVARIAN HEMORRHAGE in young women is not mentioned as a complication of long-term anticoagulant therapy either in the current textbooks of medicine, surgery, therapeutics and hematology or in recent medical[1,2] and surgical[3] reviews of the subject. Few reports have appeared in medical journals[4,5] and the bulk of the reporting has been confined to gynecologic publications.[6] This case report is presented to alert physicians to this potentially lethal complication of chronic anticoagulation.

Report of a Case

A 29-year-old woman, multipara, had rheumatic fever as a child followed by mitral valvotomy in 1972. During her last pregnancy in 1974, atrial fibrillation and transient hemiparesis developed. She was put on a long-term anticoagulant regimen of warfarin (Warfilone), 5 mg per day, and postpartum sterilization was carried out. In 1977, on the 20th day of her regular 25-day menstrual cycle she felt acute lower abdominal pain and adnexal tenderness of the left side on vaginal examination. On admission the laboratory findings included the following: prothrombin time, 23.9 seconds (control, 11.6 seconds and normal range, 9.6 to 13.0 seconds); activated partial thromboplastin time, 44.9 seconds (control, 34.5 seconds and normal range 26 to 40 seconds); and bleeding time and blood fibrinogen levels within normal limits. The platelet count was 260,000 per cu mm; hemoglobin, 11.9 grams per dl, and leukocyte count, 11,900 per cu mm.

The clinical diagnosis was acute adnexitis and concurrent acute urinary tract infection with *Klebsiella* species (untyped). Because antibiotic therapy brought no relief of the pelvic pain and her hemoglobin count dropped by 2 grams per dl, culdocentesis was done. Detection of altered blood prompted a diagnosis of ectopic pregnancy, while the possibility of adnexal hemorrhaging associated with warfarin therapy was considered unlikely. After reversal of her drug-induced coagulopathy, a laparotomy was done, which showed a hemorrhagic left adnexal mass and abundant clotted and unclotted blood in the peritoneal cavity. A diagnosis of ruptured ectopic pregnancy was made and the entire left adnexa was removed. A pathologic examination showed no evidence of pregnancy. The lesion was massive, involving intraovarian and periovarian hemorrhage, arising from a ruptured follicle, which, because of the extensive hemorrhagic destruction of its wall, was only tentatively identified as a corpus luteum. The blood clot showed degenerative changes, peripheral organization and dystrophic calcification.

Comment

Because ovarian hemorrhage in young women receiving long-term anticoagulant therapy is uncommon it tends either to be overlooked or thought to be an unlikely diagnostic possibility. In our patient, it was considered, but the diagnosis of ovarian hemorrhage was never made clinically—even at laparotomy, when ectopic pregnancy was diagnosed. Therefore, results of the pathology report came as a surprise. Understandably, the gynecologist, who had never seen this complication before, favored ectopic pregnancy, which is a well-recognized sequela of unsuccessful tubal sterilization.[7]

This rare complication of long-term anticoagulant therapy in young women deserves recognition among physicians, especially because of its diverse symptoms and signs. These include vague abdominal or pelvic discomfort, severe abdominal pain with shock, chest pain with collapse, referred

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shoulder pain and low back pain with hematuria.[6] As the mortality approaches 11 percent,[6] early diagnosis and immediate correction of the coagulopathy assume critical importance. We suggest that in young women receiving long-term anticoagulant therapy who have abdominal or pelvic pain, ovarian hemorrhage should be suspected and the patient managed accordingly, regardless of the ultimate diagnosis. It must be remembered that ovarian hemorrhage can coexist with other acute abdominal emergencies such as appendicitis.[8]

The rarity of ovarian hemorrhage in ovulating women taking anticoagulant drugs suggests that the ovary depends less critically on coagulation factors for hemostasis than other tissues and may rely more heavily on vascular readjustments. Prostaglandins, produced by the corpus luteum and the ovarian stroma,[9] may interact to shunt blood away from the ruptured corpus luteum,[10] thereby reducing the likelihood of severe hemorrhage. However, this suggestion remains speculative until ovarian hemostatic mechanisms are elucidated.

Summary

A 29-year-old woman, multipara, whose rheumatic mitral stenosis had been treated by valvotomy, was receiving long-term anticoagulant therapy following the onset of atrial fibrillation and an episode of transient hemiparesis. She later experienced lower abdominal pain and left adnexal tenderness on vaginal examination. Her condition was diagnosed sequentially as acute adnexitis and then ectopic pregnancy. Ovarian hemorrhage, clinically considered only a remote possibility, was diagnosed on pathologic examination of the left adnexa, which had been removed because of suspected ectopic pregnancy.

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Amebic Empyema

An Important Consideration in the Differential Diagnosis of Right-Sided Pleural Effusion

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ASYMPTOMATIC AMEBIASIS occurs worldwide and is often endemic in areas where sanitation levels are low.[1,2] Reports of amebic liver abscess suggest that invasive amebiasis is concentrated in comparatively few parts of the world, most notably Mexico, western South America, South Asia, and west and southwestern Africa. However, wherever amebiasis is found, invasive amebiasis may sporadically occur. In a recent series of more than 5,000 cases of invasive amebiasis from a South African referral hospital, the liver was involved in more than 40 percent of patients.[3] It is imperative that a physician maintain a high index of suspicion to diagnose this potentially fatal but easily treatable complication of amebiasis.

Report of a Case

A 43-year-old man, a Hopi Indian, came to the outpatient department of Keams Canyon Indian Hospital complaining of right-sided chest pain, nonproductive cough and a fever of two days' duration. His past medical history included a positive purified protein derivative (PPD) test in 1971. At that time the patient received isoniazid prophylaxis for a year. His travel had been limited to Arizona for the past ten years.

A roentgenogram of the chest showed pronounced right-sided pleural effusion. Temperature was 38.9°C (102°F). The patient's condition was diagnosed as bacterial pneumonia, and he was treated with a seven-day course of penicillin, given orally. Two days after completion of his therapy, a repeat roentgenogram of the chest showed persistent pleural effusion of the right side. On examination at this time, the patient was well developed, somewhat obese and in no acute

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distress. Respirations were 20 per minute, pulse 80 beats per minute and temperature 37°C (98.6°F). The left side of the chest was clear to auscultation and percussion, but on the right side decreased breath sounds and dullness to percussion at the base were noted. Examination of the abdomen showed no abnormalities.

Results of the following laboratory studies were within normal range: complete blood count, analysis of urine, total protein, albumin, bilirubin, serum transaminases and lactic dehydrogenase. Findings of a test for rheumatoid factor, an oral cholecystogram, a sputum cytologic study and sputum smears and cultures for *Mycobacterium tuberculosis* were all negative. The sedimentation rate (Wintrobe) was 48 mm per hour. Alkaline phosphatase was 236 units per dl (normal 30 to 115). Decubitus roentgenograms of the chest showed a loculated right-sided pleural effusion with very little mobile fluid. Thoracentesis was attempted unsuccessfully. The patient was presumed to have suffered a severe pneumococcal pneumonia with empyema and residual loculated sterile effusion.

Two months after onset of his illness, the patient was referred to a pulmonary specialist for evaluation of the persistent abnormality noted on repeat roentgenograms and a ten-pound weight loss. The consultant felt that the infection had been adequately treated and that the roentgenogram reflected severe pleural fibrosis from a resolved empyema. Pleural stripping was recommended if symptoms persisted.

Two weeks later the patient presented with fever and hemoptysis. A roentgenogram of the chest showed persistent effusion with pleural air fluid levels. Findings of bronchoscopy were normal; numerous attempts at thoracentesis were unsuccessful, and a thoracic computerized tomographic (CT) scan confirmed pleural loculation of fluid. Decortication of the right lung was undertaken, which showed a dense fibrous peel tightly adherent to the diaphragm. In stripping this layer from the diaphragm, a perforation was found with free communication to a liver abscess which drained a gray, pasty material. Laboratory studies done after the operation included aerobic and anaerobic cultures of the abscess material, examination of three stools for ova and parasites, and measurement of serum *Echinococcus* titer. Results of these tests were negative. However, amebic titers measured by an indirect hemagglutination test (IHA) were positive at 1:4,096. The patient was treated with metronidazole. (This therapy was begun four months after onset of symptoms.) Since the operation, the patient has done very well, is now asymptomatic and has returned to full-time employment. It is of interest that two months after treatment the titer had fallen to 1:2,048 and at five months the titer was negative.

Amebic empyema is a well-known complication of liver abscess, occurring in 7 percent to 20 percent of cases.[3,4] A recent series from Mexico City reported 88 cases with a mortality of 14 percent.[5] The clinical course was often protracted with a diagnosis being made in an average of two months. On occasion, the correct diagnosis of this disorder is made only at autopsy.[6]

Clinically, amebiasis usually begins with dysentery, which consists of frequent bowel movements with blood and mucus, abdominal pain and cramping. It may, however, present with constipation, abdominal distension, vague abdominal pain, or alternating periods of diarrhea and constipation. More than 50 percent of patients with liver abscess give no history of dysentery or diarrhea.[7] Usually, right upper quadrant pain, hepatomegaly, leukocytosis and a mild liver function abnormality are present. Many patients, as the one reported here, seem to remain almost completely asymptomatic until some catastrophic complication occurs.

Summary

Amebiasis is endemic in most areas where standards of sanitation are suboptimal. The American Indian reservation that we serve is such an area.

Our case report presents an instance of liver abscess with rupture into the pleura, an important complication of invasive amebiasis. Amebiasis should be included in the differential diagnosis of all cases of pleural effusion of the right side. A high index of suspicion in combination with serologic tests and liver scans may permit earlier diagnosis and treatment of this condition.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Rabies in Humans

To the Editor: A report in this journal in 1978 by Baraff[1] concerned a 16-year-old Mexican girl who died in Los Angeles of rabies. She had lived in an area in Mexico where rabies had been endemic and said she had not been bitten by any animals, including dogs or bats. After obtaining positive rabies antibody titers, viral cultures and immunofluorescence tests, it was found that many months before admission the girl had been bitten by a puppy who subsequently disappeared. The puppy's mother later became ill and died. The discussion commented on an incubation period of approximately one year.

The patient's family refused to accept the diagnosis of rabies and declined rabies prophylaxis.

A case of rabies in a 45-year-old man in Kentucky was reported[2] recently in which no one was able to recall any bites by animals. The man died in December 1979. In spring of the same year he had killed a groundhog that appeared to be ill.

The report gives three possible explanations for the lack of a bite history. One is that the patient could have known about a bite and did not tell anyone. Another is that the patient was unaware of a bite exposure (for example, had been bitten while sleeping). The third is the patient did not have a bite exposure to rabies.

California is second only to Texas[2] in incidence of rabies in wild animals. Nelson[3] mentions that several areas of the world are free of rabies (England, Australia and Hawaii, for example) and that some cities in the United States (New York and Philadelphia) are considered rabies-free land areas and that rabies prophylaxis for dog bites has been altered as a result of these statistics.

Previous editions of Nelson's book generally printed the World Health Organization's (WHO) recommendations on rabies prophylaxis for dog bites. WHO recommendations did not take into consideration the rabies vaccination status of the biting animal. I note with interest that the Nelson book no longer relies on the WHO recommendations as the source of the discussions on the handling of dog bites.

The purpose of this communication is to point out that rabies is still with us and that there are a minimum of four[2] reported cases of rabies in which a bite history was missing. A fifth case could be counted if one wished to refer to the case resulting from a corneal transplant.[4] It is gratifying to hear that some areas of the world are rabies free. However, this is not the case in all areas of the world, especially California and Texas as far as rabies in wild animals is concerned.

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Who's to Blame for 'The Female Fix'?

We physicians, particularly those of us who care for female patients, are continually accused of discrimination. Susan Schiefelbein, writing in the *Saturday Review,* asserts that the male-dominated medical profession is exploiting female patients as a group, overtreating them, overprescribing for them, overoperating on them. We are guilty, she says, of sexism. We take our female patients' problems lightly, while giving full credence to the complaints of men.

There is some truth in these accusations, as we will agree if we take a moment to look objectively at our own practice habits. Don't we too often listen with one ear to Mrs. Smith's long recital of her complaints, finally ending the consultation with a fatherly pat on the back and a prescription

for our favorite "harmless" tranquilizer? But when Mr. Smith comes in we listen carefully, go over him from head to toe, and promptly order electrocardiograms, x-ray studies and a screening panel of laboratory tests. In her recently published book, *The Female Fix* (Houghton Mifflin), Muriel Nellis points to these deadly statistics: Of the nation's 10 million alcoholics, half are women; 60 percent to 80 percent of mood-altering drugs are prescribed for women; women receive twice the number of drugs (often from more than one doctor) as men are given for the same symptoms. Nellis incriminates as villains the insensitive male physicians and the "underregulated" pharmaceutical industry.

Less angry and somewhat more scientific support for the contention that male physicians employ two levels of care for their male and female patients comes from a study done by Drs. Karen Armitage and Lawrence Schneidman at the University of California, San Diego. They compared the medical files of an equal number of men and women cared for by the male physicians of the local community. They zeroed in on five common complaints, including headache and low back pain. Their conclusion: "Men received more extensive workups than women in all five of the complaints. Male physicians tend to take illness more seriously in men than in women."

Why, we ask, would physicians treat women's complaints less seriously? And why do we see far more women than men in our waiting rooms? Our society accepts the premise that women are more emotional than men, that they are more given to imagined illness, that they are permitted to make an open expression of their pains and discomforts. Dr. William Barclay, editorializing in *The Journal of the American Medical Association (JAMA),* contended that women have been conditioned to behave that way: "The culture allows women to be more honest. In our society boys don't want to be thought of as 'sissies.' This may also be why men wait to see a doctor beyond the point where prudent people would."

That puts womankind back up on the pedestal. It makes us glad that women are the consumers, or at least that they direct the consumption of the major portion of our nation's health care services. Dad expects Mom to make the decision to call the doctor about Johnny's fever. Dad expects Mom to have her regular checkups, while he will come in for a physical only at his wife's insistence.

Early in their lives women are conditioned to taking pills. Owing to her reproductive activities, menstruation and childbearing, a woman is far more conscious of her bodily functions or dysfunctions. Consequently, she will more frequently be calling the doctor and she will more often be seen in his office. No wonder, then, that when a man shows up in the office we quickly conclude "There *must* be something wrong with him."

We male physicians may possess a degree of chauvinism, but none of us will agree with that pioneer of medicine Oliver Wendell Holmes, Sr., when he described woman as a "constipated biped with a backache." Nor do we share that ancient Greek notion that the uterus is the center of emotions, and that a "sickness in the womb" may result in hysteria. But let us be ready to admit that we are far more likely to make a diagnosis of conversion hysteria in a woman than in a man. And don't we often believe, and encourage our women patients to believe, that hysterectomy may be just the panacea she is looking for during that trying time called "change of life"? In so doing we subscribe to the theory that many female illnesses are psychogenic in origin and we thereby justify our liberal use of psychotropic drugs. An extensive study was done by Drs. K. Jean Lennane and R. John Lennane of New Zealand, in an effort to determine whether or not women's illnesses are psychogenic—whether they originate in the mind or the body. Their report, published in the *New England Journal of Medicine (NEJM),* was leveled at four conditions—dysmenorrhea, nausea of pregnancy, pain of labor and infant colic. They concluded that all four clinical entities have organic origins, and they sharply resented the implications, so prevalent in medical literature, that these conditions were psychogenic and the women neurotic. The late Franz Ingelfinger, former editor of the *NEJM,* in commenting on this article, said "I am struck by the Lennanes' implication that 'psychogenesis' is a derogatory label. The label of pain doesn't matter; it's real pain to the patient and warrants as much care from a physician." That concept was put to rhyme in this limerick we learned in medical school:

> There was a young lady from Deale
> Who said, "Though the pain isn't real
> When I sit on a pin
> And it punctures my skin
> I dislike what I fancy I feel!"

When Nellis puts the blame on us for the "female fix" for the overprescribing of psycho-

tropic drugs we are entitled to a rebuttal. The woman of today is demanding more health care, more pills, even more surgical procedures. The compassionate physician (and who wants one who isn't compassionate?) will reflexly reach for the prescription pad. There is a ray of hope now that through education our women patients are becoming more capable of joining in making decisions about their care. It is up to us to urge them to share this responsibility.

The last paragraph of Schiefelbein's article says it well:

> Better women's health care, it appears, will not be achieved by dogmatic physicians who regard females as helpless dependents; nor will it be received by women who regard their doctors as either patriarchal guidance counselors or chauvinistic enemies. It may be that better health care—true equality—will be achieved only when doctor and female patient alike come to regard each other as human beings. And respect each other as partners.

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Upper Airway Compression

THE SPECIALTY CONFERENCE "Vascular Compression of the Upper Airway in Children" (West J Med 132:209-218, Mar 1980) discusses a rare but important cause of airway obstruction in the pediatric age group. This article has provoked the following comments based on our experience with these lesions at Childrens Hospital of Los Angeles.

As stated, the anteroposterior and lateral films of the chest and the contrast esophagogram are the principal methods used to diagnose vascular anomalies causing tracheoesophageal compression. In the past ten years in our institution, all patients with these lesions in whom surgical therapy has been contemplated have undergone routine cineangiography.[1] This procedure, attended with little risk, permits accurate preoperative assessment of the anatomy and provides the surgeon with the foreknowledge for precise and expeditious relief of the obstruction.

Many of these patients come to surgery with critical airway obstruction, necessitating expert management of ventilation; therefore, anesthesiologists proficient in pediatric anesthesia are an essential part of the team. Diligent respiratory care in the postoperative period is essential. We usually extubate these patients in the operating room at the end of the procedure. In the intensive care unit, respiratory care includes the liberal use of humidified air and, if indicated, careful tracheobronchial aspiration.[2] To minimize the tracheal edema due to instrumentation, steroid therapy is initiated at operation and continued in the early postoperative period.

The most important point we would like to make pertains to counseling parents about this disease. A malacic segment of the trachea at the point of the vascular compression is common. Often this abnormality does not readily resolve after relieving the obstruction.[2-4] This is true especially if the compression has been very severe or long-standing. The parents should, therefore, be informed that it may be weeks or months before any noticeable clinical improvement occurs, or before the noisy breathing ceases.

We have not been able to find in the literature any detailed report of long-term results following surgical operation for these anomalies. Consequently, we have initiated a follow-up study of our patients to determine the ultimate prognosis.

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Pill Packaging

TO THE EDITOR: The pharmaceutical industry has solved the pill packaging problem in three ways: addition of cotton stuffing on top or flexible plastic inner stopper to bottles, and use of blister packaging. The most popular is the cotton, which would work infinitely better if it was inserted first, under the tablets, rather than last. When inserted at the bottom (1) the cotton would not have to be removed, (2) if a desiccant capsule is needed, it would be retained under the cotton and (3) the cotton would serve as a shock absorber for the duration of the prescription.

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Refer to: Briggs RM, Hickok DE, Rassier DS, et al: Midlevel personnel in obstetrics and gynecology practices—Cost-effectiveness and consumer benefits (Health Care Delivery). West J Med 132:466-470, May 1980

Midlevel Personnel in Obstetrics and Gynecology Practices

Cost-Effectiveness and Consumer Benefits

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Two private obstetrics-gynecology practices, in adjacent Northwest cities, which employ midlevel nurse practitioners for routine obstetric and gynecologic care were the subject of this study. At site A fees charged by the practitioner were 44 percent less than those for identical services provided by the physician. This was an attempt to pass cost savings directly to patients. At site B, fees were the same for both physician and practitioner, yielding a significant net income to the practice. At this latter site a proportion of the income was passed to patients by not *increasing office fees for the years 1975 (when the practitioner was hired) through 1977, during which time the average fees of ten other physicians increased. The study shows that the use of midlevel personnel in private offices is highly cost-effective and profitable. Ideally, this profit can be passed on to patients by reduced overall office fees.*

THE HEALTH CARE DELIVERY SYSTEM has experienced a radical change in recent years with the emergence of midlevel, nonphysician, direct-care practitioners assuming new roles in response to the need for better distribution of care and the need to retard rocketing health care costs. As Appel states, "whether cost saving will be realized and passed on to the consumer has been the subject of conjecture."[1] Several studies[2,3] have shown cost-effectiveness of midlevel personnel in prepaid medical clinics and general practice settings. The present study examines the experience of two registered nurse practitioners in different fee-for-service private obstetric and gynecologic practices in the Northwest, the incomes which they generated, and the overhead they incurred over a year's period. The study focuses on how cost savings were passed on to patients in two different ways.

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Materials and Methods

Practice Locations

The first practice setting (site A) is located in urban Seattle and consists of five board-certified obstetrician-gynecologists, who are part of a large multispecialty clinic. The practitioner (D.S.R.) is a British-trained graduate of a four-year nursing program and a midwifery post-

graduate course. Her office practice training in Seattle has been largely accomplished on the job. At her job site she has her own consultation room and assistant and uses the general examination room complex. At present, a third of her practice is routine obstetrics and two thirds of her patient visits involve annual examinations and gynecologic office procedures, including repeat Papanicolaou (Pap) smears on patients from the entire clinic. She also gives prenatal classes (two hours per week) to current obstetric patients. Previous or new patients may specifically request an appointment with the practitioner or be referred to her because generally they will be seen more quickly than by one of the physicians. Consultation with physicians for problems that the practitioner cannot manage is immediately available because a physician is always present in clinic.

The other practice setting (site B) is located in urban Tacoma, a smaller city than Seattle located 25 miles to the south. This practice consists of an office space and call-sharing group practice of three board-certified obstetric-gynecologic physicians. Each physician maintains his own financial records and pays his own expenses. For simplicity of comparison the midlevel practitioner's activities for only *one* of the three physicians (for whom she works two days per week) are the subject of this study. Therefore, her patient load and income will appear significantly less in the study than that of her Seattle counterpart. This practitioner (N.J.B.) is a certified registered nurse, who was a graduate of the Gynecorps-Women's Health Care Specialist Training program in 1975.[4] Her practice consists primarily of family planning, counseling and carrying out gynecologic office procedures. She has no clinical or teaching duties. Consultation, when urgent, is accomplished by any of the three physicians, one of whom is always present in his office; otherwise, patients are seen by one of these physicians another day. The practitioner uses the physician's office, the examination rooms and another room for consultation. After three years with one practice most of her appointments originate from specific requests by patients, although, as in site A, new patients often can be seen by her sooner than by the physicians. A comparison of sites A and B is shown in Table 1.

Analysis of Income

Information about income generated by the practitioners at both sites was obtained from a review of their records and appointment ledgers. At site A, the practitioner often saw one of the physician's patients when he was not available because of a conflicting obstetric delivery or operation. When this occurred, the practitioner was credited with her customary fee for that service.

Determining the income generated at site B was considerably easier because a separate ledger was provided for the nurse practitioner, which listed patients seen, type of visit and fee charged.

Income generated from doing Pap smears at both sites reflects only the professional fees and does not include cytology laboratory fees.

Analysis of Overhead

At site A the overhead expense was computed at 50 percent of the gross charges made by each physician throughout the entire clinic, including all specialities. The practitioner's portion of her overhead was calculated in the same way (50 percent of her charges).

Although the clinic is associated with an inpatient hospital facility, the overhead is calculated only from outpatient revenues and costs. The facilities used by the nurse practitioner would go unused if she were not present.

At site B the overhead cost charged to the practitioner was computed at 100 percent of the rent, salaries of office personnel and utilities on those days she worked alone in the office. N.J.B.,

TABLE 1.—*Comparison of Practice Sites A and B*

	Site A	*Site B*
Practice setting	Large multispeciality clinic with four obstetrician-gynecologists	Group practice with three obstetrician-gynecologists
Practitioner's training	RN, nurse-midwifery, and on-the-job	RN and Gynecorps training program
Type of patient visits	A third, obstetric; two thirds, annual examination and office gynecologic procedures	Family planning, counseling and office gynecologic procedures
Method of apportionment	Direct or referred by physician	Direct or referred by physician
Type of consultation available	Physician—immediate	Physician—immediate or the next day

TABLE 2.—*Fee Schedules at Practice Sites A and B*

Service	Site A Nurse Practitioner	Site A Obstetrician-Gynecologist	Site B Nurse Practitioner/ Obstetrician-Gynecologist
New patient visit	$12	$18	$28
Yearly examination	9-12	12-16	20
Office call	9-12	12-16	13
Insertion of intrauterine device	*	40	39
Counseling	0-12	0-30	14
(Average)†	(12)	(21)	(14)
Differential	$−9 (44 percent)		0

*D.S.R. does not insert intrauterine devices.
†Average of fees rounded to the nearest dollar.

however, regularly worked a second day when a physician was present in the office, and on these days she was charged 50 percent of the expenses.

Fee Schedules

For comparison, five common office practice activities were chosen as representative of charges levied to patients for services generally rendered by both physician and nurse practitioner. These services included (1) new patient office visit, (2) yearly examination, (3) office call (nonextended visit), (4) insertion of intrauterine device (IUD) and (5) counseling (charge per half hour).

Fee schedules on the above five services were obtained from sites A and B (both physician and practitioner) and from ten other obstetrician-gynecologists practicing in Tacoma without midlevel care practitioners for the years 1975 to 1977. This information was obtained by sending questionnaires to the 22 physicians in the Tacoma telephone directory listed as obstetrician-gynecologists. Ten of the 22 responded (45 percent).

Consultations

During the study period, consultations with physicians were reviewed when a problem beyond the capabilities of the midlevel practitioners was encountered. At site A, a month (beginning in February 1978) was monitored, and at site B, 150 consecutive patients in September 1977 were monitored to determine the rates of consultation. The rates and cost of physician consultation time (because it is nonreimbursable) were calculated and added to the practitioner's overhead.

Results

At site A a fee differential existed for patient visit charges depending on whether the patient saw a physician or the midlevel practitioner. At site B no such differential existed. Table 2 compares the MD/RN fee schedules at sites A and B.

At site A the schedules for service rendered involved a "range" which is based usually on time spent with the patient. Fees were documented by reference to day-sheets which indicated that the average charge to patients for office visits was $21.00 for the physician and $11.90 for the nurse practitioner, a difference of $9.10 or 44 percent.

Table 3 summarizes patient visits, income generated, overhead, salaries and net income to sites A and B.

The consultation rates for the practitioner at sites A and B were determined to be 8.4 percent and 10 percent, respectively. Assuming five minutes for consult at each site, $5.00 would be the cost at Site A (a sixth of $30.00—the half hour rate); 8.4 percent of 3,476 gynecology patients at $5.00 per patient amounts to $1,459.92 of additional overhead for consultations. At site B, $2.25 would be the cost (a sixth of $13.50); 10 percent of 1,738 at $2.25 per patient is $391.05 of additional overhead.

The income generated by the nurse practitioner at site A includes 2,195 gynecology visits totaling $26,120.00; 927 prenatal visits totaling $16,222.50; and 236 Pap smears totaling $2,124.00. The practitioner's total income generated was $44,467. Deducting 50 percent for overhead ($22,234) plus $1,460 for physician consultation and D.S.R.'s salary and fringe benefits, left a net income for the clinic of $2,774 for the year 1977.

From site B, the practitioner's own ledger showed a total of 1,738 patient visits from September 1976 through August 1977, which generated $24,040. Overhead came to a total of $6,307 representing supplies ($275) and office costs charged against income at a rate approximately $116 per day on days when the practitioner was in the office alone and $58 per day (50 percent) when she shared the office with the physician, plus $391 for physician consultation. Salary on a per diem basis was $65 per day in September 1976 and $70 per day after October 1, 1976, for a total of $6,270 per year. By subtracting N.J.B.'s salary and overhead charged to her from the income she generated we determined a net income to the practice of $11,072 ($27,680 extrapolated to a 40-hour week).

Table 4 compares the "frozen" fees for five types of visits charged by both physician and

practitioner at site B with the average of those fees charged by ten other obstetrician-gynecologists in Tacoma over the same period (1975 to 1977) who did not employ midlevel practitioners.

In 1975 the fees charged by the site B physician and the midlevel practitioner were about average for the community except that their fee for IUD insertion was 22 percent higher than the ten-physician average, and their counseling fee was 35.7 percent lower. By 1977 the ratio had changed. Fees in the community had increased as much as a third for some services (counseling) while those of site B had remained the same. In 1977, site B fees ranged from 3.7 percent less (IUD insertion) to 58.7 percent less (for a half hour of counseling) than the average of those in the community.

TABLE 4.—*Average Fee Schedule at Site B and for Ten Other Obstetrician-Gynecologists in Tacoma, 1975-1977*

Type of Visit	*Site B*	*Average of 10 Physicians*
	1975	1975
New patient	$28.00	$25.11
Yearly examination	20.50	20.31
Office call	12.50	13.22
Insertion of IUD	38.50	31.38
Counseling (½ hour)	13.50	21.00
	1976	1976
New patient	28.00	29.11
Yearly examination	20.50	21.24
Office call	12.50	14.55
Insertion of IUD	38.50	39.19
Counseling (½ hour)	13.50	30.22
	1977	1977
New patient	28.00	30.22
Yearly examination	20.50	21.95
Office call	12.50	16.50
Insertion of IUD	38.50	40.00
Counseling (½ hour)	13.50	32.77

IUD = intrauterine device

Discussion

The effectiveness of midlevel nurse practitioners in obstetrics and gynecology has been shown by "process" measures of care including patient acceptance[5-9] and performance of procedures such as IUD insertions.[10] Outcome of health in patients managed by nurse practitioners and physicians also has proved comparable.[3,11] Cost-effectiveness has been shown for private practices[2,12] and prepaid health maintenance organizations[13] in specialities other than obstetrics and gynecology. In the present study, measures of care were not assessed other than cost savings in the private practice setting.

The subject of cost-effectiveness of midlevel personnel has been argued extensively and approached in various ways. In evaluating cost-effectiveness, two pitfalls must be avoided. Care must be taken to include in the overhead all nonreimbursable activities, such as cost of consultation time for the nurse practitioner with the physician.[14] One must also avoid the danger of equating cost-effectiveness with saving of physician time without showing that physician time is used more significantly elsewhere.

In this study, as in others,[2,3,12] the cost-effectiveness has been shown based on income from each of the practices. This calculation has included the cost for physician consultation at a rate which was 10 percent or less at each site and was not considered a significant nonreimbursable cost factor (see Table 3). Because of the fee-for-service nature of the practice sites, neither laboratory nor medication cost was examined.

Conclusion

The methods by which cost savings have been passed on to patients are quite different for each of the two sites. At site A the net profit to the

TABLE 3.—*Profit Generated by Employing Midlevel Nurse Practitioners*

	Site A	*Site B*	
Study period	January 1977-December 1977	September 1976-August-1977	
Hours employed per week	40	16	40*
Total patients seen	3,476	1,738	4,345
12-month income generated	$44,467	$24,040	$60,100
Overhead			
Practitioner	$22,234	$ 6,307	$15,768
Physician consultation	$ 1,460	$ 391	$ 977
Salary and fringe benefits	$18,000	$ 6,270	$15,675
Net income to site†	$ 2,774	$11,072	$27,680

*Figures in this column extrapolated to a 40-hour week, including physician consultation time.
†Calculated by subtracting overhead, salary and fringe benefits from income generated.

practice was minuscule compared with the income generated because the cost savings were passed directly on to patients and overhead expenses were relatively high. At site B, a rather unique way of passing cost savings on to patients was achieved by *not* increasing office fees for three years. During these three years the average fee charged for five measurements of care by ten other obstetrician-gynecologists in Tacoma (who did not employ midlevel personnel) increased each year (Table 4). By 1977 all five fees charged at site B were *less* than the average charged by the ten other obstetrician-gynecologists in the same city. Thus, total health care cost at site B was lower in 1977, thereby benefiting *all* patients at that site. It is our contention that the use of midlevel personnel generates profits and keeps down all office fees, and that this best serves patients at a time when health costs are dramatically rising.

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Propranolol for Lowering Serum Calcium

AN UNUSUAL GROUP of patients are those with hyperthyroidism who have hypercalcemia. If you control the hyperthyroidism with antithyroid drugs, of course you can control the hypercalcemia, but the control of hyperthyroidism takes weeks if not a month or two. If a patient is symptomatic with a calcium level of 12 or 13 ml per dl, you can give propranolol intravenously or even propranolol orally in higher doses. It very nicely and acutely lowers the serum calcium. You stop the infusion, and back up goes the calcium. It is felt that the effect of excessive thyroid hormone is on the bone cells directly, stimulating resorption activity of bone cells, and that this is mediated through the beta-adrenergic system. Hence, propranolol can rapidly reverse that effect. . . . We do not see these patients very often, but it is a very nice effect if one is faced with such a patient.

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Commentary

Prevention: An Idea Whose Time Has Come?

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THE SURGEON GENERAL'S REPORT on Health Promotion and Disease Prevention claims that preventive medicine's (PM) time has come.[1] This remains to be seen. As an idea, prevention in medicine has been with us for a long time.[2] Although support for PM has waxed and waned, it may be on the rise again. However, the likelihood that PM will remain permanently in our national health policy depends on two factors: (1) whether advocates of preventive medicine can effectively develop new measures for applying the principles of PM to current health problems and (2) whether its supporters can expand the base of ideological and financial support to include a broader spectrum of medical professionals and the general public.

The Current View of Preventive Medicine

Most people understand preventive medicine in terms of traditional public health activities such as immunizations for infants and children; control of fresh water supplies; safe sewage disposal; assurance that foods are safe and drugs are effective; and detection and control of infectious diseases. These activities are routinely and competently carried out in the nation's many local health departments. However, despite their enormous importance in preventing disease, these efforts are generally taken for granted by both the public and by our colleagues in curative medicine.

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More visible programs developed by those practicing preventive medicine include detecting and controlling chronic diseases, particularly cancer, heart disease and stroke. These programs sometimes use new cost-effective screening and detection procedures to discover persons in the asymptomatic stages of these diseases.[3] Other PM projects receiving increased attention involve geriatrics, maternal and child nutrition, and prevention of alcohol and drug abuse.

Some New Directions

During the past 15 years the view of preventive medicine as public health, even with its expanding programs for control of chronic disease, has been broadened considerably. One new focus involves an attempt to identify and reduce chronic disease risk factors. Encouraged by developments such as the Health Hazard Appraisal[4] and the Lifetime Health Monitoring Program[5] this strategy aims at identifying, quantifying, and reducing or eliminating—through personal behavior changes—the risk factors that contribute to premature death from heart disease, cancer, accidents and stroke. For example, heart disease risk factors (such as abnormal blood pressure level, increased plasma cholesterol level, excessive weight and sedentary life-style) have been studied in some detail; and there is mounting evidence that the burden of mortality from heart disease can be decreased by reducing these risk factors.[6]

There is also growing interest by preventive medicine practitioners in identifying and reducing risk factors involving large populations such as whole communities or groups of employees. Oc-

cupational and environmental risk factors that are out of the control of individual persons may soon be identified, measured, and reduced by epidemiologically scaled preventive strategies. A recent Department of Health, Education and Welfare (DHEW) conference reviewed the state of the art for these strategies and suggested some approaches for starting such programs in occupational settings.[7]

Health promotion, representing a quantum leap from the idea of disease prevention, is another area receiving more attention by practitioners of preventive medicine.[8] Advocates of health promotion believe that health is not simply the absence of illness but a measurable, ascending hierarchy of states of mental, physical and social fitness. Although assessment of risk may be a first step, health promotion aims at more than reducing premature mortality in asymptomatic persons. Health promotion advocates also believe that higher states of health can be attained by disciplined activities such as programmed exercise.

Finally, preventive medicine, both as idea and medical specialty, has become associated to some degree with Community Medicine. Although not easily defined as either a medical specialty or an academic discipline, Community Medicine has as a major concern the research of health services. This includes the systematic study of medical education, the measurement and assurance of medical care delivery, the evaluation of alternative forms of health care to groups of people, and the development of cost-containment programs in health care delivery.

Many questions remain about the developing strategies of preventive medicine. Although alluring on its face value, will the claim that assessment of health risks can prevent premature death be supported by prospective studies? Is the idea of health as a hierarchy of measurable states only applicable to individual persons, or can a strategy be developed for entire communities or population groups as well? What bioethical considerations must be weighed in considering these preventive strategies, especially those aimed at asymptomatic persons? Before we embrace unequivocally the new PM approaches, we need answers to these and other serious questions. Fortunately, there is evidence that the first condition is being met to insure that preventive medicine will become a permanent part of our national health policy. However, what about the second condition? A broader base of support must emerge if preventive medicine is going to endure.

Support for Preventive Medicine

Preventive medicine is still lacking political and economic clout. Only 4 percent of each federal health care dollar is targeted specifically for PM activities.[9] And the 1.5 percent of the nation's 350,000 practicing physicians who are engaged in full-time preventive medicine practice (aerospace medicine, public health, general preventive medicine and occupational medicine) is hardly a significant proportion.[10]

Preventive medicine's influence is also limited because it requires less of the high-level technology associated with the more visible image of curative medicine. The low-key profile of preventive medicine and its practitioners tends to limit its attractiveness to medical students and residents: The drama of curative medicine, captured by television's scalpel-toting heroes, is poorly challenged by a specialist in preventive medicine armed only with clipboard and calculator. Finally, although clinicians in all specialties—particularly in primary care—advocate the ideals of PM, they are too widely dispersed across the spectrum of clinical specialties to achieve the unity necessary to increase PM's political influence.

What Needs to Be Done?

Although the picture is not bleak, it is hardly one for unrestrained optimism. Several things need to be done. First, those who embrace preventive medicine, either as a full-time calling or as an important part of their clinical practice, must become active advocates of preventive medicine. I am not suggesting a propaganda campaign —those supporting the tradition of preventive medicine as a rigorous approach for solving health care problems would rightfully reject this tactic. Instead, I recommend educational efforts aimed at both the public and at professional colleagues. Such a campaign should point out preventive medicine's past successes as well as its current and emerging programs. If such an educational campaign can be mounted, the diffusion of those practicing PM within curative medicine might prove an unexpected advantage; a broader base of support could be developed within these curative specialties.

Second, carefully prepared research proposals

must be developed to evaluate the new strategies of preventive medicine, and funding agencies, both public and private, must be encouraged to support such research. The DHEW report mentioned earlier is not intended to be viewed as a list of specific objectives or preludes to action by the federal government. Rather, the report should be interpreted as a roadmap to which state and local agencies can turn for direction. However, it would be irresponsible for the federal government to raise expectations for PM without providing some hard evidence of its own commitment.

Third, those groups claiming to represent preventive medicine, such as the Association of Teachers of Preventive Medicine, the American College of Preventive Medicine and the American Public Health Association, must become more active. They must appeal for financial support for research, training programs in preventive medicine, and demonstration projects in health promotion and disease prevention. Although these groups have advocated the philosophy of preventive medicine at the national level, I encourage them to focus more energy at state and local levels. Here they need to convince legislators that preventive medicine makes not only good health care sense but good budgetary sense as well, particularly when the long view is taken.

Conclusion

Preventive medicine *may* be an idea whose time has come. Recent developments have given preventive medicine some of the tools it has needed to offer practical solutions to serious health problems. However, more determined efforts are needed to insure that preventive medicine will become a significant and permanent part of our national health policy.

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THE XXVIII ANNUAL CONVENTION of the Medical Society of the United States and Mexico will convene in Guadalajara, Jalisco, Mexico, November 12 through 15, 1980. For further information, write Mrs. Carolyn Parsons, Executive Secretary, 3161 North Pantano Road, Tucson, AZ 85715.

Refer to: Barton C: Placebo analgesia (Clinical Note). West J Med 132:474, May 1980

Clinical Note

Placebo Analgesia

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THE PRODUCTION of analgesia by placebos has previously been explained in terms of psychological expectation. However, recent experiments have implicated a distinct physiological mechanism involving the newly discovered endogenous opiates (endorphins). Very little is known about factors affecting endorphin action although increased blood levels of this substance have been found associated with pain.

Levine and co-workers[1,2] at the University of California, San Francisco, reasoned that if placebo analgesia is a result of endorphin release then naloxone (the specific opiate antagonist) should reverse or block it. They tested their hypothesis on patients recovering from wisdom tooth extraction. In the double-blind study, patients were given a placebo and asked to rate their pain on a scale from 0 to 10. When compared with their predrug pain rating, patients predictably fell into two groups, placebo responders and placebo nonresponders. Nonresponders had a pain rating twice that of responders. Naloxone was then given to both groups with the result that the mean pain rating for placebo responders increased to the same level as that of nonresponders. This suggested that most of the analgesic effect of placebo is naloxone reversible, for naloxone had no effect in nonresponders. Also, if naloxone was given before placebo, the probability of responding to placebo was greatly reduced.

These studies indicate that endorphin activity accounts for placebo analgesia. This is consistent with the concept that the brain has an intrinsic mechanism for dealing with pain. That there is such a system is supported by observations that midbrain electrical stimulation produces analgesia which is reversed by naloxone in humans. These experiments not only add to our understanding of placebo analgesia, they also suggest the potential for utilizing the brain's intrinsic mechanism for dealing with pain. Because the response to pain potentially includes activation of a pain suppression system, the act of giving a substance or carrying out a procedure such as acupuncture that is expected to relieve pain may enhance this natural pain suppression system.

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Clinical Note

'Regression' of Atheroma

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IN THE COURSE of following cardiac patients in marathon training, we may have observed the first case of "regression" of atheroma in coronary angiograms.

The man, who is now 68 years old, complained of disabling angina when he was 61. The chest pain had progressed over a period of 13 years in spite of a limited walking program of less than 2 miles per day. Angiograms at that time showed a precarious, high-grade narrowing of 95 percent in the circumflex (CIRC) branch of the left coronary artery. His exercise prescription was increased to a goal of 10 kms per day of walking and jogging. Seven years later, follow-up angiograms showed that the CIRC narrowing had regressed from 95 percent to 50 percent (Figures 1 and 2).*

During this time an area of 75 percent narrow-

*The coronary angiograms and clinical data were supplied by Dr. M. Sanmarco of the Cardiac Rehabilitation Program, Rancho Los Amigos Hospital, Downey, California.

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Figure 1.—Left coronary angiograms in left anterior oblique (LAO) showing 95 percent narrowing of circumflex branch before training, age 61, 1972.

Figure 2.—Left coronary angiograms (LAO) showing regression of the circumflex narrowing from 95 percent to 50 percent after running 10,000 miles in units of 10 kms, age 68, 1979.

ing in the right coronary artery regressed to less than 30 percent (Figures 3 and 4).

He is now without symptoms and running 10 kms per day at a ten-minute-per-mile pace. He is a nonsmoker who has logged 10,000 miles in units of 10 kms over seven years. This same exercise prescription has been used by many of the cardiac patients who have reached the 42-km marathon distance. However, he has not attempted a marathon run because of orthopedic complaints.

The 1979 Cardiac Division of the Honolulu

Figure 3.—Right coronary angiograms (LAO) showing 75 percent narrowing before aerobic training, 1972.

Figure 4.—Right coronary angiograms showing less than 30 percent narrowing after training, 1979.

Marathon has brought the new total of "cardiac marathoners" to 159. They now represent 700 patient-years. Follow-up shows that 152 are alive and running. We continue to follow the entire group.

ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles they consider to be important in other journals. These titles together with a brief assessment of the articles are published for the information of our readers.*

Dysmenorrhea: Treatment With an Antiprostaglandin

Larkin RM, Van Orden DE, Poulson AM, et al

Obstetrics & Gynecology
54:456-459, Oct 1979

DISCIPLINES: Obstetrics, Gynecology, Surgery, General and Family Practice

READABILITY: Very good

Ibuprofen (Motrin), an antiprostaglandin, in doses of 400 mg every four hours, was found to give remarkable relief of the pain of dysmenorrhea in 82 percent of the patients tested. The authors recommend its use in preference to aspirin or indomethacin.

Paired Controlled Study of Vaginal and Abdominal Delivery of the Low Birth Weight Breech Fetus

Duenhoelter JH, Wells CE, Reisch JS, et al

Obstetrics & Gynecology
54:310-313, Sep 1979

DISCIPLINES: Obstetrics, Gynecology, General Surgery, General and Family Practice

READABILITY: Very good

In a paired, controlled, retrospective study comparing vaginal with abdominal delivery of low birth weight breech fetuses the incidence of fatal asphyxia, trauma and intracranial hemorrhage was significantly higher in vaginal deliveries. The authors conclude that for the low birth weight fetus delivery by cesarean section is preferable.

Experience With Teenage Pregnancy

Hutchins FL, Kendall N, Rubino J

Obstetrics & Gynecology
54:1-5, Jul 1979

DISCIPLINES: Family Practice, Obstetrics, Gynecology, Pediatrics

READABILITY: Excellent

Teenage pregnancies, with their inherent risks of preeclampsia, low birth weight infants, and increased neonatal and fetal mortality, are not primarily a medical problem. Teenage pregnancy is a sociologic problem say these authors. The solution: prevention. The goal: better educational programs introduced before teenage years.

Changing Trends and Prognostic Features in Endometrial Cancer Associated with Exogenous Estrogen Therapy

Robboy SJ, Bradley R

Obstetrics & Gynecology
54:269-277, Sep 1979

DISCIPLINE: Obstetrics, Gynecology, Pathology, General and Family Practice

READABILITY: Very good

This study, from Harvard Medical School, compared the clinical course and the prognosis of the endometrial cancers in separate cohorts of users and nonusers of estrogens. They concluded that in estrogen users the tumors were more highly differentiated, rarely was there invasion of the myometrium, the cancers were detected earlier, and the overall 5-year and 10-year survival rates were higher.

Minilaparotomy for Female Sterilization

Penfield, AJ

Obstetrics & Gynecology
54:184-188, Aug 1979

DISCIPLINES: Obstetrics, Gynecology, Surgery, General and Family Practice

READABILITY: Very good

Literally thousands of sterilizations through the direct approach of "minilaparotomy" have been done in other parts of the world. The author believes it will be widely used in the United States because it can be done under local anesthesia in an outpatient setting, is relatively simple, has few complications and does not require expensive equipment. The limitations are outlined.

The Kevorkian Curette—An Appraisal of Its Effectivness in Endometrial Evaluation

Ferenczy A, Shore M, Guralnick M, et al

Obstetrics & Gynecology
54:262-267, Aug 1979

DISCIPLINES: Obstetrics, Gynecology, General and Family Practice, General Surgery

READABILITY: Very good

The authors recommend a wider use of the Kevorkian curette for obtaining intrauterine biopsy specimens because (1) it is a safe, simple, and accurate office procedure, (2) the instrument is reusable, rather than disposable, (3) it provides the advantage of histiologic over cytologic diagnosis and (4) it allows for identification of the location from which the tissue is obtained.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Patients, Regulation, and Health Care

Journal of the Indiana State Medical Association
73:88-90, Feb 1980

DISCIPLINES: All

READABILITY: Good

In 1976 an attempt was made in Louisiana to reduce Medicaid costs by reducing the number of drugs paid for under the program. A probable result, according to this article, was a substantial increase in expenses for hospital and other services. Based on a study funded by the National Pharmaceutical Council, the article's findings are a good illustration of the interdependent nature of the various segments of health care.

—MALCOLM S. M. WATTS, MD
San Francisco

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Wednesday

8:30 am-5:00 pm House of Delegates

Thursday

8:15 am Introduction
Robert K. Borron, MD
Program Chairman

8:30 am The Adolescent
Kermit E. Krantz, MD
Professor and Chairman
Department of Obstetrics and Gynecology
Professor of Anatomy
The University of Kansas Medical Center

9:15 am Paget's Disease of Bone—Diagnosis and Therapy
Louis V. Avioli, MD
Professor of Medicine
The Jewish Hospital of St. Louis;
Washington University School of Medicine
St. Louis

10:30 am The Diagnosis and Therapy of Secondary Amenorrhea
Martin Farber, MD
Associate Professor
Department of Obstetrics and Gynecology
Director
Division of Reproductive Endocrinology
New England Medical Center Hospital, Boston

11:30 am Principles of Antibiotic Prophylaxis in Surgery
E. Patchen Dellinger, MD
Assistant Professor
Department of Surgery
University of Washington School of Medicine

1:30 pm Evaluation of the Patient
Kermit E. Krantz, MD

3:00 pm Case Presentations
(Question and Answer Period)

4:00 pm Adjournment

Friday

8:15 am Introduction
Robert K. Borron, MD

8:30 am Senile and Postmenopausal Osteopenia
Louis V. Avioli, MD

9:30 am Female Anatomy of Sex
Kermit E. Krantz, MD

10:45 am The Diagnosis and Management of Severe Necrotizing Soft-Tissue Infections
E. Patchen Dellinger, MD

11:30 am The Diagnostic Evaluation and Surgical Management of Congenital Anomalies of the Müllerian Ducts
Martin Farber, MD

1:30 pm Overview of Sexually Transmitted/Associated Diseases Other Than Gonorrhea and Syphilis
Stephan Billstein, MD
Associate Director
Health Information & Services
Roche Laboratories
San Francisco

3:00 pm Case Presentations
(Question and Answer Period)

4:00 pm Adjournment

Saturday

8:30 am-3:00 pm Closing Session, House of Delegates

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For information contact:

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Telephone: (208) 344-7888

in memoriam

California Medical Association

Bick, Guenther Claus, Pacific Palisades. Died February 20, 1980 in Pacific Palisades, aged 60. Graduate of Universität Köln Medizinische Fakultät, Köln, Prussia, 1944. Licensed in California in 1956. Dr. Bick was a member of the Los Angeles County Medical Association.

Bolen, Darrell Wesley, Torrance. Died January 10, 1980, aged 42. Graduate of Stanford University School of Medicine, Palo Alto, 1964. Licensed in California in 1965. Dr. Bolen was a member of the Los Angeles County Medical Association.

Cole, Frank, Culver City. Died December 16, 1979, aged 83. Graduate of Johann Wolfgang Goethe-Universität, Medizinische Fakultät, Frankfurt-am-Main, Prussia, 1926. Licensed in California in 1935. Dr. Cole was a member of the Los Angeles County Medical Association.

Everett, Marie G., Anaheim. Died January 31, 1980 of subdural hematoma, aged 50. Graduate of the University of Miami School of Medicine, Coral Gables, 1961. Licensed in California in 1962. Dr. Everett was a member of the Orange County Medical Association.

Holman, John Crafford, jr., San Diego. Died February 26, 1980, aged 74. Graduate of Tulane University School of Medicine, New Orleans, 1934. Licensed in California in 1939. Dr. Holman was a retired member of the San Diego County Medical Society.

Inman, Verne T., San Francisco. Died February 5, 1980 in San Francisco, aged 74. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Dr. Inman was an associate member of the San Francisco Medical Society.

Kinney, William M., Riverside. Died January 21, 1980 in Riverside, aged 74. Graduate of Northwestern University Medical School, Chicago, 1932. Licensed in California in 1943. Dr. Kinney was a retired member of the Riverside County Medical Association.

Laing, Donald Reid, Pasadena. Died April 1, 1980, aged 78. Graduate of Rush Medical College, Chicago, 1934. Licensed in California in 1936. Dr. Laing was a member of the Los Angeles County Medical Association.

Quinn, Thelma, Los Altos Hills. Died March 12, 1980 at Stanford University Medical Center, aged 54. Graduate of the University of Utah College of Medicine, Salt Lake City, 1948. Licensed in California in 1949. Dr. Quinn was an associate member of the Santa Clara County Medical Society.

Smythe, Violet Pence, Bakersfield. Died in July 1979 in Bakersfield of heart disease, aged 77. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1938. Licensed in California in 1938. MD degree from California College of Medicine, 1962. Dr. Smythe was a retired member of the Kern County Medical Society.

Soghor, Samuel, Los Angeles. Died January 29, 1980, aged 74. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Dr. Soghor was a member of the Los Angeles County Medical Association.

Wandruff, Benjamin, Tracy. Died January 27, 1980 in Tracy of myeloproliferative syndrome, aged 74. Graduate of the University of Michigan Medical School, Ann Arbor, 1944. Licensed in California in 1945. Dr. Wandruff was a member of the San Joaquin County Medical Society.

Washington State Medical Association

Elden, C. Arthur, Bothell. Died February 21, 1980, aged 84. Graduate of the University of Rochester School of Medicine and Dentistry, 1930. Licensed in Washington in 1946. Dr. Elden was a member of the King County Medical Society.

Hathaway, Stillman J., Tacoma. Died March 16, 1980, aged 87. Graduate of the University of Minnesota Medical School, Minneapolis, 1919. Licensed in Washington in 1947. Dr. Hathaway was a member of the Medical Society of Pierce County.

Powers, Edward J., Kirkland. Died February 23, 1980, aged 58. Graduate of the St. Louis University School of Medicine, 1946. Licensed in Washington in 1947. Dr. Powers was a member of the King County Medical Society.

Watkins, Charles W., Vancouver. Died in January 1980, aged 57. Graduate of the St. Louis University School of Medicine, 1951. Licensed in Washington in 1958. Dr. Watkins was a member of the Clark County Medical Society.

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Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

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Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE).

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: In clinical studies in 1493 patients, adverse effects considered related to cefaclor therapy were uncommon and are listed below.

Gastrointestinal symptoms occurred in about 2.5 percent of patients and included diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions were reported in about 1.5 percent of patients and included morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occurred in less than 1 in 200 patients.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory tests results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [070379R]

* Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[8]

Note: Ceclor® (cefaclor) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

References

1. Antimicrob. Agents Chemother., *8*:91, 1975.
2. Antimicrob. Agents Chemother., *11*:470, 1977.
3. Antimicrob. Agents Chemother., *13*:584, 1978.
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5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II: 880 Washington, D.C.: American Society for Microbiology, 1978.
6. Antimicrob. Agents Chemother., *13*:861, 1978.
7. Data on file, Eli Lilly and Company.
8. Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr., and J.E. Bennett), p. 487. New York: John Wiley & Sons, 1979.

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

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(Continued on Page 24)

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

HANDBOOK OF PEDIATRICS—Thirteenth Edition—Henry K. Silver, MD, Professor of Pediatrics, University of Colorado School of Medicine; C. Henry Kempe, MD, Professor of Pediatrics and Microbiology, University of Colorado School of Medicine; and Henry B. Bruyn, MD, Clinical Professor of Medicine and Pediatrics, University of California School of Medicine, San Francisco, Director of Child Health and Disability Prevention, City and County of San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1980. 735 pages, $9.50.

HANDBOOK OF POISONING: Prevention, Diagnosis & Treatment—Tenth Edition—Robert H. Dreisbach, MD, PhD, Clinical Professor of Environmental Health, School of Public Health and Community Medicine, University of Washington, Seattle, and Professor (Emeritus) of Pharmacology, Stanford University School of Medicine. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1980. 578 pages, $9.00.

ISOZYMES: Current Topics in Biological and Medical Research—Volume 3—Editors: Mario Rattazzi, Department of Pediatrics, Children's Hospital, State University of New York, Buffalo; John G. Scandalios, Department of Genetics, North Carolina State University, Raleigh; and Gregory S. Whitt, Department of Genetics and Development, University of Illinois, Urbana, Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1979. 212 pages, $22.00.

NEWBORN BEHAVIORAL ORGANIZATION: NURSING RESEARCH AND IMPLICATIONS—Birth Defects: Original Article Series, Volume XV, Number 7, 1979: Editors: Gene Cranston Anderson, RN, PhD, Professor and Research Coordinator, The J. Hillis Miller Health Center, University of Florida; and Beverly Raff, PhD, Director of Health Personnel Development, The National Foundation; Consulting Editor: Mitzi Duxbury, PhD, FAAN, Associate Professor, Assistant Dean, University of Minnesota; Associate Editor: Patricia Carroll, MS, The National Foundation-March of Dimes. Alan R. Liss, Inc., 150 Fifth Ave., New York City (10011), 1979. 228 pages, $24.00.

PATIENT RECORDS CONTROL—dap/Doctors' Administrative Program—Avis Bosshart Ziegler. Medical Economics Company, Book Division, Box 157, Florence, KY (41042), 1979. 216 pages, $10.00 (soft cover).

PENETRANCE AND VARIABILITY IN MALFORMATION SYNDROMES—Part B of ANNUAL REVIEW OF BIRTH DEFECTS, 1978—Editors: James J. O'Donnell, MD, Assistant Professor of Ophthalmology, University of California, San Francisco; and Bryan D. Hall, MD, Professor of Pediatrics, University of California, San Francisco; Associate Editor: Natalie W. Paul, The National Foundation; Assistant Editor: Marilyn P. Orlando, The National Foundation-March of Dimes. Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1979. 382 pages, $42.00.

PLACEBOS AND THE PHILOSOPHY OF MEDICINE—Clinical, Conceptual and Ethical Issues—Howard Brody, MD, PhD, Resident in Family Practice, University of Virginia Medical Center. The University of Chicago Press, 5801 S. Ellis Ave., Chicago (60637), 1980. 164 pages, $13.50.

Rx: A PRESCRIPTION FOR WELLNESS—A Brochure for Patients—Ronald J. Pion, MD. Triseme Corporation, Hollywood, CA (90028), 1979. 10 pages, for information and ordering, write: Ronald Pion, MD, Triseme Corporation, 1438 North Gower, Hollywood, CA 90028.

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(Continued on Page 26)

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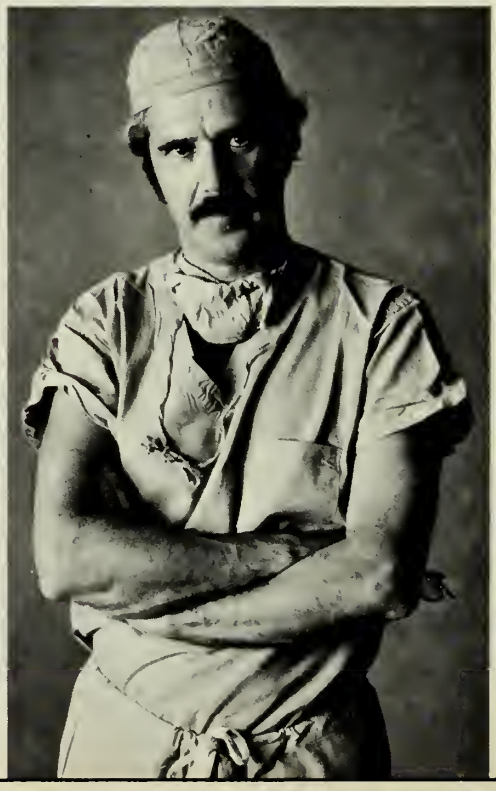

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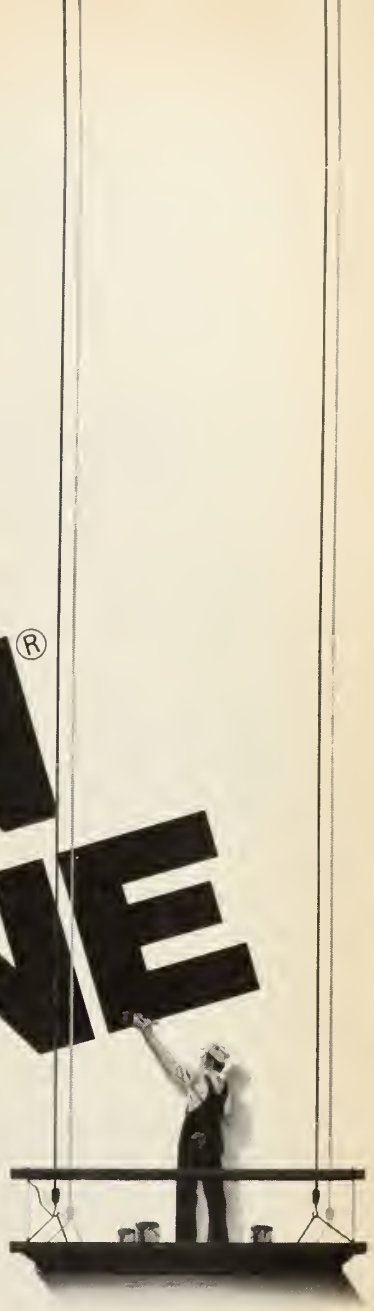

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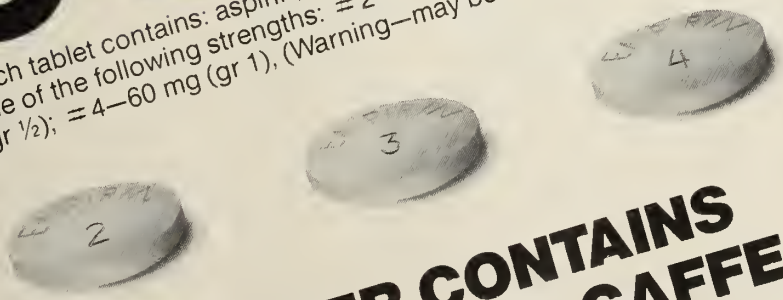

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ANESTHESIOLOGY

June 5-8—**California Society of Anesthesiologists—Annual Scientific Assembly.** MGM Grand Hotel, Reno. Thursday-Sunday. 23 hrs. Contact: Mr. N. R. Catron, Exec. Dir., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

October 3-5—**Anesthesia Specialties.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Del Monte Hyatt, Monterey. Friday-Sunday. 10½ hrs. $90, AEF member; $165, nonmember. Contact: Walter H. Comer, MD, AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

October 26-28—**Anesthesia and Cardiopulmonary Disease.** Calif. Society of Anesthesiologists at Del Monte Hyatt, Monterey. Sunday-Tuesday. 11 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

CANCER

May 26-27—**American Society of Clinical Oncology.** Town and Country Hotel, San Diego. Monday-Tuesday. Contact: A. Van Horn, III, Exec. Dir., 435 N. Michigan Ave., Chicago 60611.

October 24-26—**Enzymes and Related Proteins in the Diagnosis and Prognosis of Neoplastic Diseases.** UCSD at Vacation Village, San Diego. Friday-Sunday.

EMERGENCY MEDICINE

May 15—**ENT Emergencies.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

May 19-23—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 40 hrs. $300.

May 27-31—**American College of Emergency Physicians, California Chapter—1980 Scientific Assembly.** ACEP, Calif. Chap., and UCSD at Hotel del Coronado, Coronado. Tuesday-Saturday. Contact: UCSD.

June 4-8—**Seminar in the Sierra: Advanced Course in Emergency Medicine.** Doctor's Essential Services, Inc.; Providence Hospital, Oakland; and Emergency Physicians, San Leandro, at Stanford Sierra Lodge, Fallen Leaf Lake, Lake Tahoe. Wednesday-Sunday. 21 hrs. $260. Contact: Maureen E. Dvorak, DES, 897 MacArthur Blvd., San Leandro 94577. (415) 632-1504.

June 5—**Prehospital Care for the Acutely Ill or Traumatized Child—An Emergency Approach.** See Pediatrics, June 5.

June 17—**Death in the Emergency Department.** St. John's Hospital and Assn. for Emergency Physicians for Ventura and Santa Barbara Counties at St. John's Hospital, Oxnard. Tuesday; 8:00 p.m. 1½ hrs CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

June 18-20—**Radiology in the Emergency Room Department.** UCSF at Fairmont Hotel. Wednesday-Friday.

June 19—**Plastic Surgery in the Emergency Department.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

June 20-22—**Recognition and Management of Poisonings and Toxicological Emergencies.** UCSF, S.F. Bay Area Reg. Poison Control Ctr., Am. Assn. of Poison Control Ctrs. and Am. Academy of Clinical Toxicology at Jack Tar Hotel, San Francisco. Friday-Sunday. 17 hrs. Contact: Dr. Kenneth W. Lem, UCSF, San Francisco 94143. (415) 666-4194.

June 23-27—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

June 27-28—**Ophthalmology and ENT for Emergency Room Physicians.** PMC. Friday-Saturday. 12 hrs.

(Continued on Page 34)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717. (714) 833-5414, Fee and Information office or (714) 833-5526, 5542, Continuing Education in Health Sciences.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

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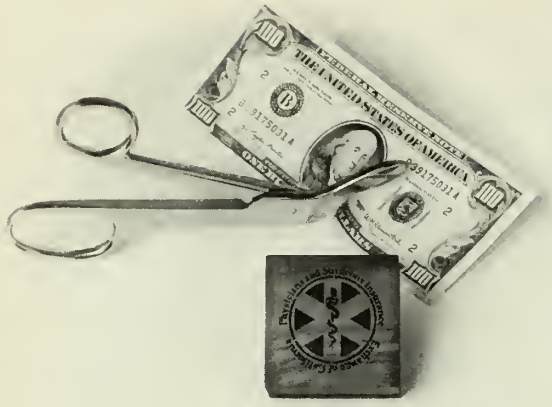

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(Continued from Page 32)

July 14-18—**Medical Management of EMS Systems.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs.

July 21-25—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

July 25-27—**Advanced Cardiac Life Support Provider, Recertification and Instructor Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, Education Dept., 2310 Mason St., San Francisco 94133. (415) 956-5900.

August 11-15—**Postgraduate Institute for Emergency Physicians, Symposium I:** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

September 18—**Abdominal Trauma.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

October 13-17—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

October 16—**Dermatology in the Emergency Department.** UCSD. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

October 20-31—**Intensive Review of Emergency Medicine.** USC. Two weeks.

MEDICINE

May 15-17—**Acute Myocardial Infarction.** PMC at St. Francis Hotel, San Francisco. Thursday-Saturday. 15 hrs.

May 16-18—**Cardiac Rehabilitation.** International Medical Education Corp. at Jack Tar Hotel, San Francisco. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

May 19-24—**4th Bi-Annual Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday.

May 30—**Team Approach to Arthritis.** PMC and Arthritis Foundation. Friday. 6 hrs. $85.

May 30-31—**Prevention and Treatment of Venous Thromboembolism.** Cedars-Sinai Medical Center, Los Angeles. Friday-Saturday. 9 hrs. $150. Contact: Lore Kahane, Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Rm 2049, Los Angeles 90048. (213) 855-5547.

May 31-June 1—**Pediatric Dermatology.** UCLA. Saturday-Sunday.

May 31-June 1—**Kidney Disease—20th Annual Scientific Symposium.** Kidney Foundation of Southern Calif. at Bonaventure Hotel, Los Angeles. Saturday-Sunday. Contact: Micki Faris, Kidney Fndn. of So. Calif., 6820 La Tijera Blvd., Suite 111, Los Angeles 90045. (213) 641-8152.

June 2-6—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday. 34 hrs.

June 3-October 14—**Internal Medicine Review.** UCLA. Tuesday evenings.

June 7—**Current Concepts in Cardiac Rehabilitation.** Am. Heart Assn., Greater L.A. Affiliate, at Biltmore Hotel, Los Angeles. Saturday. 6 hrs. $60, AHA member; $70, nonmember. Contact: Jan Stein, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

June 9-13—**Advances in Internal Medicine.** UCSF. Monday-Friday. 34 hrs.

June 11-14—**7th Annual Symposium on Clinical Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Wednesday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 18—**The Diagnosis and Management of the Newborn With Cardiorespiratory Disease.** American Heart Assn., Greater Los Angeles Affiliate, at New Otani Hotel, Los Angeles.

Wednesday. 6 hrs. $50, member; $60, nonmember. Contact: Mary Frances Flynn, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

June 20-21—**Medical Knowledge Self Assessment—Group C.** American College of Physicians and PMC at Hyatt Regency, San Francisco. Friday-Saturday. Contact: PMC.

June 21-22—**American Association for the Study of Headache.** Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: S. Diamond, MD, Exec. Sec., 5252 N. Western Ave., Chicago 60625.

June 27-29—**Hepatobiliary Disease in Clinical Practice.** American College of Physicians at Holiday Inn on Union Square, San Francisco. Friday-Sunday. 15 hrs. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

July 8-10—**Podiatric Dermatology.** STAN. Tuesday-Thursday. 17 hrs.

July 11-13—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Hyatt Regency, San Francisco. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

July 12-19—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 23 hrs. $290.

July 29-August 3—**5th Annual Postgraduate Course and Workshop in Medical Mycology-Dermatomycology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Tuesday-Sunday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 2—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

August 7-9—**Society for Pediatric Dermatology—5th Annual Meeting.** SPD and STAN at Doubletree Inn, Monterey. Thursday-Saturday. 15 hrs. $150, members; $200, nonmembers. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

August 8-9—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Saturday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

August 13—**Calcium Metabolism—Its Diagnosis and Management.** LLU. Wednesday. 4 hrs. $30.

August 14-16—**A Pan-Pacific Conference on Tuberculosis in the 80s.** Hawaii Thoracic Society, Am. Lung Assn. of Hawaii, Hawaii Dept. of Health and Univ. of Hawaii at Ala Moana Hotel, Honolulu. Thursday-Saturday. $35. Contact: Hawaii Thoracic Society, 245 N. Kukui St., Honolulu 96817.

August 15-17—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

September 5—**13th Annual Symposium on Kidney Disease—Endocrine and Metabolic Functions of the Kidney.** Kidney Foundation of Northern Calif. at Fairchild Auditorium, Stanford Univ. Sch. of Med., Stanford. Friday. 6 hrs. $45. Contact: William Arnopp, Exec. Dir., KFNC, 100 S. Ellsworth Ave., Ste. 305, San Mateo 94401. (415) 347-6646.

September 18-19—**Hypertension.** UCD at Sahara, Lake Tahoe. Thursday-Friday. 15 hrs.

September 25-26—**Annual Physicians' Symposium.** American Heart Assn., San Francisco Chapter, at San Franciscan Hotel, San Francisco. Thursday-Friday. Contact: Kari Olila, AHA, 421 Powell St., San Francisco 94102. (415) 433-2273.

September 26-27—**American Society of Internal Medicine.** Islandia Hyatt, San Diego. Friday-Saturday. Contact: ASIM, 2550 M St. NW, Suite 620, Washington, DC 20037.

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September 26-28—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Hyatt on Union Square, San Francisco. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

September 27—**Management of Chronic Lung Disease.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

October 4-11—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

October 8—**Endocrine Review.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. Contact: Janie Sternal, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

October 8—**Modern Therapy for Common Dermatologic Problems.** LLU. Wednesday. 4 hrs. $30.

October 10-12—**Chest Disease Symposium.** The Cypress Foundation and UCSF at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Robert S. Meyer, Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

Ocober 13-17—**An Advanced Course for Internists.** STAN. Monday-Friday. 25 hrs. $290.

October 18-25—**Cardiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $325.

October 27-30—**Practical Electrocardiography Course for Primary Physicians.** Memorial Hospital Medical Center-UCI Center for Health Education at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: Center for Health Education. 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

OBSTETRICS AND GYNECOLOGY

June 5-7—**Gynecologic Urology: Theory and Practice, Basic and Advanced.** Mem. Hosp. Med. Ctr.-UCI Ctr. for Health Education at Inn at the Park, Anaheim. Thursday-Saturday.

20 hrs. $300. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 16-18—**Nutritional Care of High-Risk Obstetrical Patients and High-Risk Infants.** STAN. Monday-Wednesday. 18 hrs. $20.

August 9-15—**Reproductive Endocrinology, Infertility and Contraception.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

August 23-28—**Practical Management of the Infertile Couple.** See Of Interest To All, August 23-28.

September 12-13—**Environmental Hazards in Pregnancy: A Clear and Present Danger.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 12 hrs.

PEDIATRICS

May 21-25—**Pediatrics for the Primary Care Physician.** UCD at Red Lion Motor Inn, Sacramento. Wednesday-Sunday. 18 hrs.

May 24-26—**Northern California Chapter, American Academy of Pediatrics—Annual Spring Meeting.** Del Monte Hyatt House, Monterey. Saturday-Monday. 8 hrs. $100, members; $125, nonmembers. Contact: Beverly Busher, NCCAAP, 422 Alexander Ave., Larkspur 94939. (415) 924-9613.

May 31-June 1—**Pediatric Dermatology.** See Medicine, May 31-June 1.

June 5—**Prehospital Care for the Acutely Ill or Traumatized Child—An Emergency Approach.** L.A. Pediatric Society; Calif. Chapter 2, AAP; Paramedic Training Institute; L.A. Co. Dept. of Health Services at Hilton, Los Angeles. Thursday. $150. Contact: L.A. Pediatric Society, P.O. Box 2022, Inglewood 90305.

June 6-8—**Connective Tissue Disease.** American Academy of Pediatrics and Children's Hospital of Los Angeles at Bonaventure Hotel, Los Angeles. Friday-Sunday. Contact: Judy C. Hambourger, Cont. Ed., AAP, P.O. Box 1034, Evanston, IL 60204.

June 14-21—**Pediatric Workshop.** USC at Royal Lahaina, Maui, Hawaii. One week. 22 hrs. $325.

June 16-18—**Nutritional Care of High-Risk Obstetrical Patients and High-Risk Infants.** See Obstetrics and Gynecology, June 16-18.

June 18—**The Diagnosis and Management of the Newborn With Cardiorespiratory Disease.** See Medicine, June 18.

August 2—**Pediatric Dermatology.** See Medicine, August 2.

September 18-20—**Pediatric Urology.** UCD at Holiday Inn, Napa Valley. Thursday-Saturday. 12 hrs.

October 3-4—**Pediatric Topics: Neonatology.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 10 hrs. $85.

October 25—**Hearing Impaired Child.** Peninsula Hospital, Burlingame. Saturday. Contact: Susan Norrell, c/o Radiology Dept., Peninsula Hosp., 1783 El Camino Real, Burlingame 94010. (415) 697-4061, ext. 479.

October 25-November 1—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center-UCI Center for Health Education and L.A. Pediatric Society at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 21 hrs. $200. Contact: Center for Health Education, MHMC, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

PSYCHIATRY

June 4—**Movement Disorders—Update 1980.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 6 hrs. $65. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

June 21-22—**Intellect and Illness.** UCLA. Saturday-Sunday.

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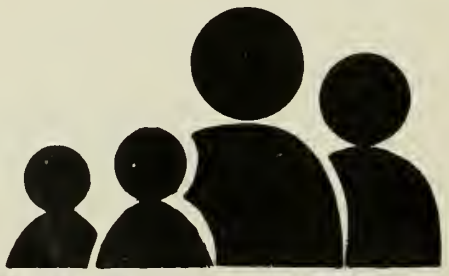

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June 23-27—**Comparative Psychotherapies.** USC at Hilton, San Diego. Monday-Friday.

August 1-3—**Child Psychiatry.** UCD at Holiday Inn-on-the-Beach, Monterey. Friday-Sunday.

October 25—**Cognitive Prospectives in Psychiatry.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

RADIOLOGY AND PATHOLOGY

May 17—**Recent Advances in Pathology.** UCSF at Hyatt on Union Square, San Francisco. Saturday. 8 hrs. $90.

May 28-30—**Present Concepts in Diagnostic Radiology.** Letterman Army Medical Center, San Francisco. Wednesday-Friday. 18 hrs. Contact: R. S. Pakusch, MD, or D. Kumar, MD, Dept. of Radiology, Letterman Army Med. Ctr., San Francisco 94129. (415) 561-3761.

June 6-8—**Spring Diagnostic Ultrasound Conference—5th Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 17 hrs. $250. Contact: Nathan Green, MD, 15107 Vanowen St., Van Nuys 91405.

June 16-25—**Radiology of Bone and Joint Disease.** UCSD at Hotel del Coronado, Coronado (June 16-19) and Kauai Surf Resort Hotel, Kauai, Hawaii (June 23-25). 7 days. 29 hrs. $500 (or $300 for first part; $200, second part).

June 18-20—**Radiology in the Emergency Room Department.** See Emergency Medicine, June 18-20.

June 22-27—**Pathology of the Lung.** UCSD. One week. 50 hrs. $450.

August 9-16—**Radiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

September 27-October 4—**Diagnostic Radiology.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

October 10-12—**Society of Nuclear Medicine—5th Annual Western Regional Meeting.** Airport Marriott, Los Angeles. Friday-Sunday. Contact: SNM, P.O. Box 40279, San Francisco 94140. (415) 647-5909.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

May 15-17—**Nasal Plastic and Reconstructive Surgery.** PMC at Clift Hotel, San Francisco. Thursday-Saturday. 15 hrs. $250.

May 18-22—**American Urological Association.** Hilton, San Francisco. Sunday-Thursday. Contact: AUA, 1120 N. Charles St., Baltimore, MD 21201.

May 29-31—**Oto '80.** Project HEAR at St. Francis Hotel, San Francisco. Thursday-Saturday. 24 hrs. $485. Contact: Judy Staton Thielke, Project HEAR, 1801 Page Mill Rd., Palo Alto 94304. (415) 494-2000.

May 30-31—**Prevention and Treatment of Venous Thromboembolism.** See Medicine, May 30-31.

June 3-6—**1st Annual Verne T. Inman Lectureship and 15th Annual Scientific Program of the LeRoy C. Abbott Orthopaedic Society.** UCSF. Tuesday-Friday. 14 hrs. Contact: Judy Baca, Alumni Sec., UCSF, Room U471, San Francisco 94143. (415) 666-1166.

June 5-6—**Neurosurgery Postgraduate Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Friday. 17 hrs. $225.

June 6-7—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

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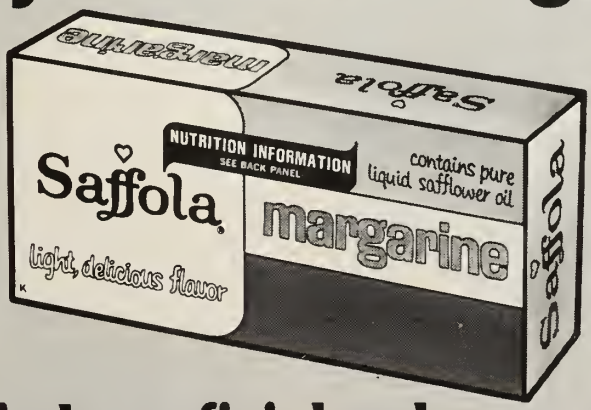

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June 7—**Glaucoma Surgery Course.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

June 7-13—**Orthopedic Review Course.** UCSF at Hyatt on Union Square, San Francisco. One week. 50 hrs.

June 11—**Problems in Postoperative Management and the Surgical Intensive Care Unit.** LLU. Wednesday. 4 hrs. $30.

June 14—**Evaluation of the Trauma Patient.** UCD at Rancho Murieta Country Club, Rancho Murieta. Saturday. 7 hrs. $50.

June 14-21—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $325.

June 19-20—**Office Orthopedics.** USC. Thursday-Friday.

June 19-21—**Highlights of Ophthalmology.** PMC at Hyatt Regency, San Francisco. Thursday-Saturday. $225.

July 9—**The Management of Acute Trauma.** LLU. Wednesday. 4 hrs. $30.

July 12-19—**Cardiovascular Medicine and Surgery: An Advanced Course.** See Medicine, July 12-19.

September 2-5—**IV International Symposium on Facial Nerve Surgery.** Ear Research Institute, Los Angeles. Tuesday-Friday. Contact: Facial Nerve Symposium, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

September 10—**Hematuria—An Approach to Diagnosis and Therapy.** LLU. Wednesday. 4 hrs. $30.

September 13-20—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

September 18-20—**Pediatric Urology.** See Pediatrics, September 18-20.

September 19-20—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

September 25-28—**Cost Effective Urological Diagnosis and Treatment.** Western Section, Am. Urological Assn. and AUA at Marriott's Rancho Las Palmas Resort, Palm Springs. Thursday-Sunday. Contact: Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

September 26-27—**Vitrectomy.** UCSD at Vacation Village, San Diego. Friday-Saturday.

September 28-October 2—**American Academy of Otolaryngology.** Convention Center, Anaheim. Sunday-Thursday. Contact: AAO, 15 Second St. SW, Rochester, MN 55901.

OF INTEREST TO ALL PHYSICIANS

May 16-18—**2nd Annual National Symposium on Sexuality and Disability.** UCSF at Claremont Hotel, Berkeley. Friday-Sunday. Contact: UCSF Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94122. (415) 666-3904.

May 17—**Integrated Health Care.** Alameda-Contra Costa County Medical Assn. and UCSF at Kaiser Center, Oakland. Saturday. 6 hrs. $75. Contact: John B. Whalen, MD, 3300 Elm St., Oakland 94609. (415) 653-6320.

May 17-18—**Advanced Therapeutics in Clinical Nutrition.** St. Francis Memorial Hospital and American Society of Parenteral and Enteral Nutrition at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: Elena Tinloy, PharmD, St. Francis Mem. Hosp., P.O. Box 7726, San Francisco 94120. (415) 775-4321, ext. 3323.

May 18-23—**Fingers-to-the-Toes: An Orthopaedic Approach for the Family Practitioner.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Friday.

May 19-24—**7th Annual Family Practice Refresher Course.** UCLA and Santa Monica Hospital Medical Center at Sheraton-Miramar, Santa Monica. Monday-Saturday. Contact: UCLA.

May 21—**Frontiers in Clinical Genetics: Biology and Ethics.** General Hospital Ventura County at Casa Sirena and Lobster Trap, Channel Islands Harbor, Oxnard. Wednesday. 6 hrs. Contact: Harvey M. Harris, MD, Dept. of Med. Ed., Gen. Hosp. Ventura Co., 3291 Loma Vista Rd, Ventura 93003. (805) 654-3637 or 654-3638.

May 31-June 1—**Family Practice Symposium—8th Annual.** So. Calif. Permanente Medical Group at Marriott Hotel, Newport Beach. Saturday-Sunday. Contact: Catherine Andrews, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4516.

June 2-7—**Third Annual Gerontology Institute—Session I.** San Jose State Univ., San Jose. Monday-Saturday. Contact: Office of Cont. Ed., San Jose State Univ., San Jose 95192. (408) 277-2182.

June 7-8—**Psychiatry for the Primary Care Physician.** UCLA. Saturday-Sunday.

June 7-8—**Nutrition: Myths and Realities.** UCSF and Institute for the Study of Human Knowledge at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

June 11-13—**Clinical Application of Hyperbaric Oxygen—5th Annual Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 24 hrs. Contact: G. B. Hart, MD, Dir., Baromedical Dept., Mem. Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801.

June 13-15—**American Medical Association Regional Meeting.** Hyatt on Union Square, San Francisco. Friday-Sunday. Contact: AMA, Dept. of Meeting Services, 535 N. Dearborn St., Chicago 60610. (312) 751-6503.

June 16-21—**Family Practice Refresher Course.** UCI at Marriott Inn, Newport Beach. Monday-Saturday. 50 hrs. $375. Contact: UCI (714) 833-5526.

June 21-22—**Risk—And the Health of the Public.** UCSF. Saturday-Sunday. $100. Contact: UCSF, Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94143. (415) 666-3904.

July 9-13—**Human Sexuality.** Associated Alumni, UCI, at Del Monte Hyatt, Monterey. Wednesday-Sunday. 15 hrs. Contact: June Harris, Associated Alumni, UCI-CCM, 101 City Dr. S., Bldg. 53, Orange 92668. (714) 634-0152.

August 4-9—**Third Annual Gerontology Institute—Session II.** San Jose State Univ., San Jose. Monday-Saturday. Contact: Office of Cont. Ed., San Jose State Univ., San Jose 95192. (408) 277-2182.

August 10-14—**Western Hemisphere Nutrition Congress VI.** American Medical Association, American Institute of Nutrition, Nutrition Society of Canada, at Biltmore Hotel, Los Angeles. Sunday-Thursday. Contact: AMA, Dept. of Foods and Nutrition, 535 N. Dearborn St., Chicago 60610.

August 14-17—**Sexuality.** Orange County and American Urological Associations at Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

August 16-27—**23rd Annual Hawaii Refresher Course.** USC at Sheraton-Waikiki Hotel, Maui. 12 days. 39 hrs. $350.

August 17-18—**Computers in Medicine—Applications of Artificial Intelligence Techniques.** STAN. Sunday-Monday. 11½ hrs. $40. Contact: William J. Clancey, AIM Tutorial Coordinator, Rm. TC 117, Div. of Gen. Int. Med., Stanford Univ. Sch. of Med., Stanford 94305.

August 23-28—**Practical Management of the Infertile Couple—4th Annual Edward Tyler Symposium.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. Saturday-Thursday. 16 hrs. $225. Contact: Jetset Tours, 2029 Century Park East, Suite 2130, Los Angeles 90067.

August 24-29—**Family Practice Refresher Course—8th Annual.** UCD at Del Monte Hyatt, Monterey. Sunday-Friday.

September 24-28—**Human Dimensions in Medicine.** UCSD at Vacation Village, San Diego. Wednesday-Sunday.

September 25—**Venereal Disease.** Calif. Venereal Disease Controllers' Assn. and CMA at Tiburon Lodge, Tiburon. Thursday. Contact: Manuel De Pinna, CMA.

September 26-27—**Dermatology for Physicians in Family Practice.** UCD at Holiday Inn, Napa Valley. Friday-Saturday.

October 11—**Ophthalmology for the Family Physician.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

October 13-16—**Fifth Annual Family Practice Update.** LLU. Monday-Thursday. 31 hrs. $200.

October 16-18—**West Coast Counties Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 28-31—**American Academy of Occupational Medicine.** Hyatt Regency, San Francisco. Tuesday-Friday. Contact: AAOM, 150 N. Wacker Dr., Chicago 60606.

October 30-November 1—**Postgraduate Institute on Nutrition.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

May 28—**Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday, 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

June 6-9—**Alaska State Medical Association Annual Meeting and Sports Medicine.** Mt. McKinley Village Lodge. Friday-Monday. Contact: Martha McDermaid, Alaska State Medical Association, 4107 Laurel St., Anchorage, AK 99504. (907) 277-6891.

June 19—**Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

MONTANA

May 28-30—**Nuclear Medicine for Internists—Univ. of Wash. Internal Medicine Review Sessions.**

May 28, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 29, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

May 30, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 52 West Pine, Missoula, MT 59801. (406) 549-3782.

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June 11-13—**Transient Ischemic Attack and Stroke; Seizure Disorders—Univ. of Wash. Internal Medicine Review Sessions.**

June 11, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

June 12, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-3782.

June 13, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

IDAHO

May 19—**Hypertension and Pregnancy—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 20—**Dysmorphology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony's Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

August 22—**Intermountain Infectious Disease Symposium.** Idaho Falls. Friday. Intermountain Experience Center. Contact: DeVon Hale, MD, P.O. Box 1602, Idaho Falls, ID 83401. (208) 529-0072.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

MEDICINE

September 5-6—**Current Perspectives on Rheumatology.** Ashland, Friday-Saturday. Ashland Hills Inn. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

November 14-15—**Symposium on Critical Care Medicine.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

October 23-25—**Northwest Review of Obstetrics & Gynecology.** Portland, Thursday-Saturday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

PHYSICAL MEDICINE AND REHABILITATION

May 30-31—**Annual Meeting of the Northwest Association of Physical Medicine and Rehabilitation** (Main Topics: Neurogenic Bladder, Pain Control; and Medical Review)—Newport, Friday-Saturday. Embarcadero Resort. Contact: John E. Stanwood, MD, Physical Therapy Dept., Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave., Portland, OR 97210. (503) 229-8040.

PSYCHIATRY

September 13—**Movement Disorders.** Portland, Saturday. OMA Headquarters, 5210 SW Corbett Ave., Portland, OR 97201. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

June 17-20—**American College of Physicians Review Course.** Portland, Tuesday-Friday. Jantzen Beach Thunderbird. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 26-28—**Symposium on Sports Medicine.** Eugene, Thursday-Saturday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

September 18-19—**Dermatology for the Non-Dermatologist.** Portland, Thursday-Friday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

(Continued on Page 42)

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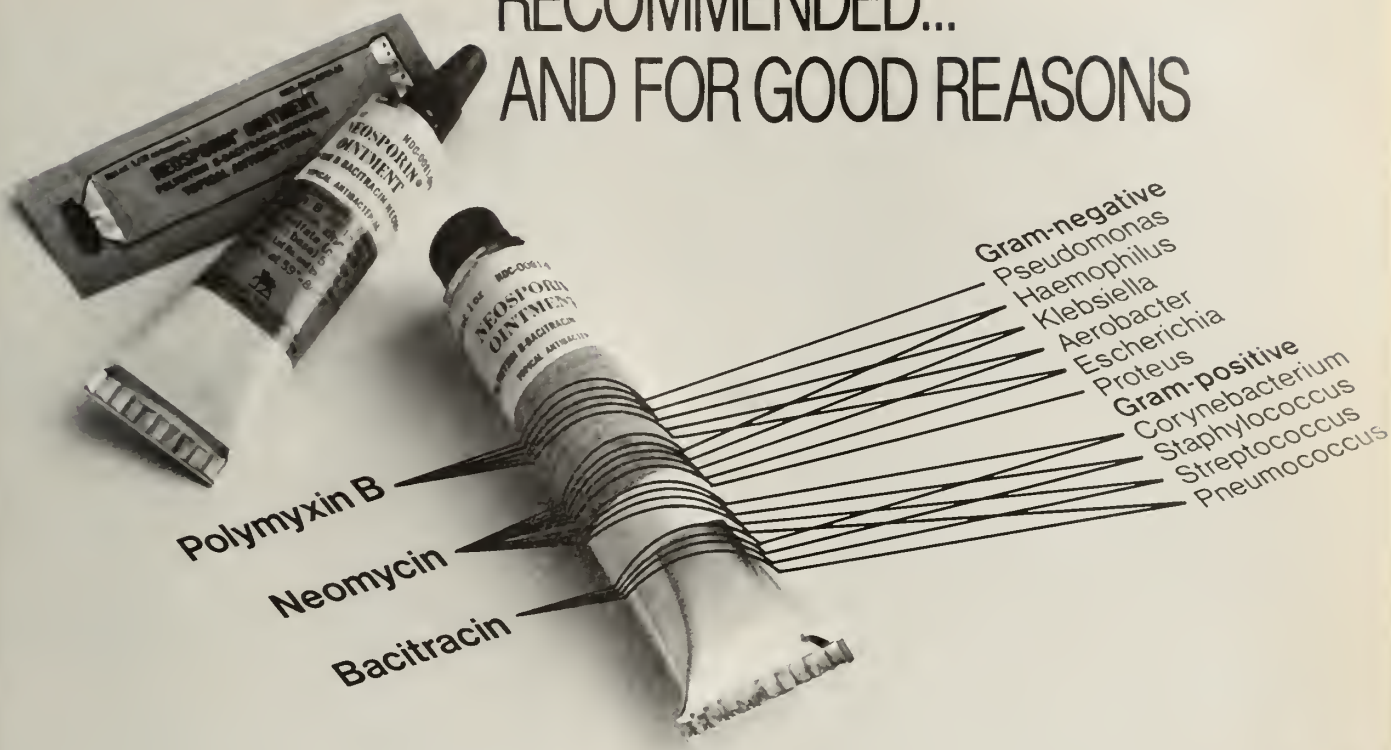

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When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

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(Continued from Page 40)

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

May 16-17—**Rest of Our Lives.** Seattle. Friday-Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 16-17—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 19—**Ophthalmology Program.** Seattle. Monday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education & Training Dept., 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, Ext. 686.

May 20—**Hypertension and Pregnancy—Univ. of Wash. OB-GYN Sessions** (Spokane). 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 22-23—**Adolescent Medicine.** Seattle. Thursday-Friday. Child Development and Mental Retardation Center. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 30—**Ophthalmology in Family Practice.** Seattle. Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 5-6—**Physician/Patient Relationship.** Gleneden, Oregon. Thursday-Friday. Salishan Resort, Gleneden, Oregon. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 6-7—**Workshops in Musculoskeletal Disease.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Renal Disease.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 12-13—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Olympic Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 19-20—**Perspectives in Clinical Chemistry.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 23—**Basic Concepts of Immunology and Their Application—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

June 26-27—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 28-July 5—**Alaska Cruise—Emergency Medical Care: Trauma, Orthopedics and Surgery; Biomedical History.** 8 days. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

July 25-26—**Seafair II Anesthesia Meeting**—Washington State Society of Anesthesiologists. Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Sandra McDonald, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

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UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

May 20

SPONSOR: University of Utah (With State of Utah Emergency Medical Services Bureau)
TITLE: **Burn Critical Care**
LOCATION: Garfield Memorial Hospital, Panguitch
FEE: None
CREDIT: 2 hours
CONTACT: Stanley J. Bezek, Jr., MD (801) 676-8842

May 21-23

SPONSOR: Ogden Surgical Society
TITLE: **35th Annual Medical Meetings**
LOCATION: Weber State College, Ogden
FEE: Members—no fee
Non-members—$10.00 registration fee
CREDIT: 25 hours
CONTACT: Ralph Foley, MD (801) 621-5400

May 23

SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—New Concepts in the Management of Congestive Heart Failure**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: 3 hours
CONTACT: Stan Everett (801) 350-1004

June 12-14

SPONSOR: Carbon Hospital, Price
TITLE: **4th Annual Castle Country Symposium**
LOCATION: Price
FEE: To be announced
CREDIT: 12 hours
CONTACT: Mary Louise Ghirardelli (801) 637-1123

June 16-19

SPONSOR: University of Utah
TITLE: **Physicians' Workshop on Alcoholism**
LOCATION: UU
FEE: $200.00
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

June 16-20

SPONSOR: VA Regional Medical Education Center
TITLE: **Legal Medicine**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Lew Erschler (801) 582-1565, Ext. 1100

July 10-11

SPONSOR: University of Utah
TITLE: **3rd Annual Birth Defects, Mental Retardation and Medical Genetics Symposium**
LOCATION: A. Ray Olpin Hall, University of Utah
FEE: $40.00
CREDIT: 13 hours
CONTACT: John Carey, MD (801) 581-8943

August 7-8

SPONSOR: VA Regional Medical Education Center
TITLE: **Geriatric Assessment**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Barbara Cordell, RN (801) 582-1565, Ext. 1100

August 26-28

SPONSOR: VA Regional Medical Education Center
TITLE: **Conflict, Confrontation, and Stress**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Alan Lundgren (801) 582-1565, Ext. 1100

September 11

SPONSOR: Rocky Mountain Center for Occupational and Environmental Health
TITLE: **Occupational Health for the 1980's**
LOCATION: Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
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LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
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OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UU: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-9, 1980, McKinley Village Lodge.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: 1981—date and place to be announced.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 24-27, 1980, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 13-17, 1980, Pacific Beach Hotel, Waikiki.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1980, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 2-4, 1980, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 16-18, 1980, MGM Grand, Las Vegas.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 7-9, 1980, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-31, 1980, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 30-October 3, 1980, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 2-5, 1980, Thunderbird at Jantzen Beach, Vancouver, WA.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 23-27, 1980, Snow King Inn, Jackson.

September 12

SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Medical Management of Ischemic Heart Disease**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: 3 hours
CONTACT: Stan Everett (801) 350-1004

September 22-25

SPONSOR: VA Regional Medical Education Center
TITLE: **Sexual Health**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: George Keiser, PhD (801) 582-1565, Ext. 1100

October 1-2

SPONSOR: VA Regional Medical Education Center
TITLE: **Geriatric Assessment**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Barbara Cordell, RN (801) 582-1565, Ext. 1100

October 16

SPONSOR: LDS Hospital (with Intermountain Thoracic Society, Utah Heart Association and University of Utah)
TITLE: **Postgraduate Course—Pulmonary Heart Disease**
LOCATION: LDSH
FEE: To be announced
CREDIT: 6 hours
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

December 12

SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Hypertension**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: To be announced
CONTACT: Stan Everett (801) 350-1004

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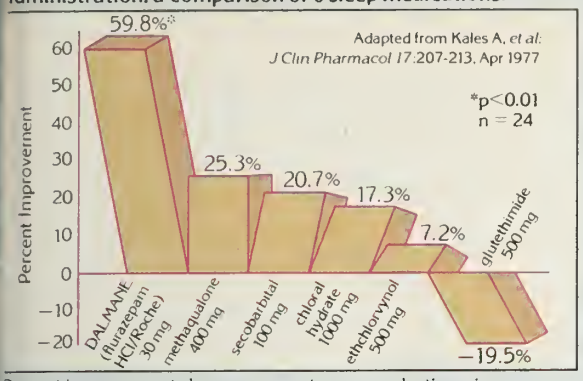

Percent improvement shown represents mean reductions, in minutes, of insomnia in the parameter of total wake time.

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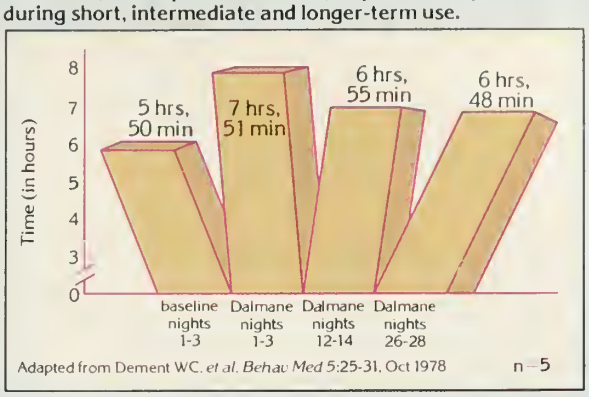

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REFERENCES:
1. Kales A, *et al: J Clin Pharmacol 17*:207-213, Apr 1977
2. Dement WC, *et al: Behav Med 5*:25-31, Oct 1978
3. Kales A, *et al: Clin Pharmacol Ther 19*:576-583, May 1976
4. Frost JD Jr, De Lucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979

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- ☐ Monitor response to therapy and, based upon patient reassessment, determine need for continuing medication on an individual basis.
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- ☐ Caution patients against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle shortly after ingesting the drug. In addition, as with all CNS depressants, patients may have reduced motor performance while on hypnotic therapy and should be advised accordingly.
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Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

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Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
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Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, e.g., excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
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The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed double-spaced throughout (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

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1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 292:444-456, Apr 26, 1978

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 7: 76-79, Sep 1978

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, IL, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, MA, Publishing Sciences Group, Inc, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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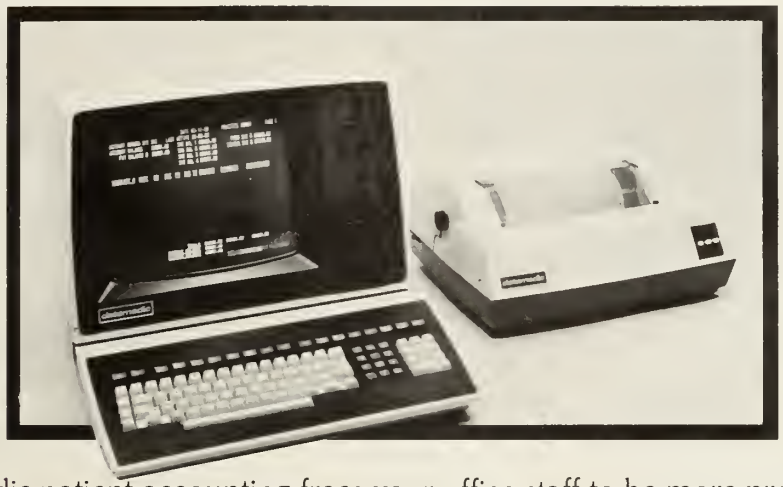

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ibuprofen

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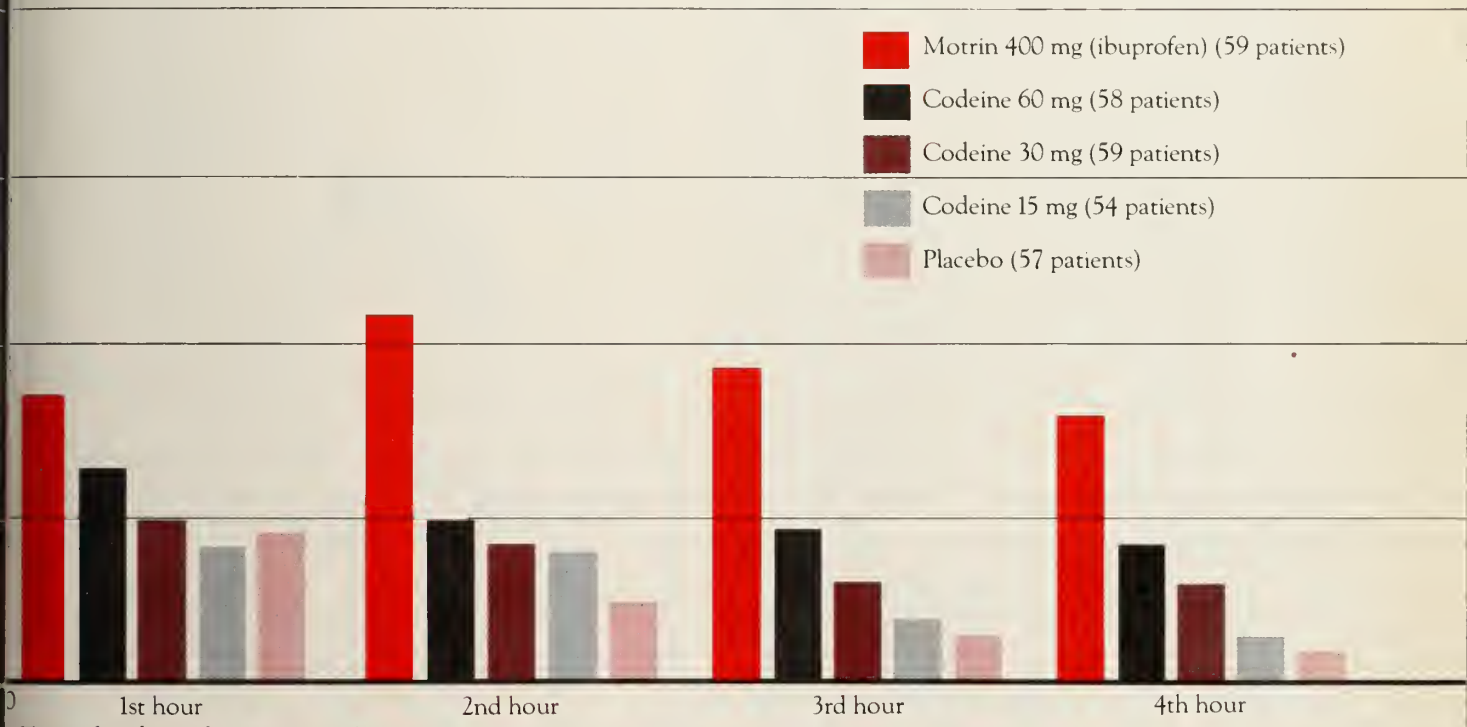

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A well-tolerated, nonnarcotic prescription for mild to moderate pain

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ibuprofen, Upjohn

- Not a narcotic • Not addictive • Not habit forming • Acts peripherally
- Relieves pain rapidly • Indicated in acute and chronic pain • Well tolerated
- The most common side effect with *Motrin* is mild gastrointestinal disturbance.

Please turn the page for a brief summary of prescribing information.

Upjohn

Motrin® (ibuprofen) now proved an effective analgesic for mild to moderate pain

Motrin® Tablets (ibuprofen, Upjohn)

Indications and Usage: Relief of mild to moderate pain.

Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness,* headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis, including flares of chronic disease: Suggested dosage is 300, 400 or 600 mg t.i.d. or q.i.d.
Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for relief of pain.

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The stress-secretion relationship in duodenal ulcer*

The best available evidence suggests that anxiety and emotional tension stimulate acid-pepsin secretion.[1] Also, the development of an ulcer crater in predisposed individuals, or the aggravation of ulcer symptoms, is often typically preceded by a stressful event or situation. *Anxiety* in particular seems to play a determining role in the course and prognosis of the disease, as well as its etiology.

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The pituitary gland plays a key role in the neurohormonal response to emotional stress, leading to an increase in gastric secretion.[2]

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*Librax has been evaluated as possibly effective for this indication.

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1. Isenberg J, Richardson CT, Fordtran J: Pathogenesis of peptic ulcer, chap. 46, in *Gastrointestinal Disease*, ed. 2, edited by Sleisenger MH, Fordtran JS. Philadelphia: W.B. Saunders Company, 1978, vol. 1, pp. 800, 801.
2. Sun DCH: Etiology and pathology of peptic ulcer, chap. 27, in *Gastroenterology*, ed. 2, edited by Bockus HL, *et al.* Philadelphia: W.B. Saunders Company, 1974, pp. 579.

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and the potent antisecretory and antispasmodic actions of QUARZAN® (clidinium Br/Roche)

Initial Rx

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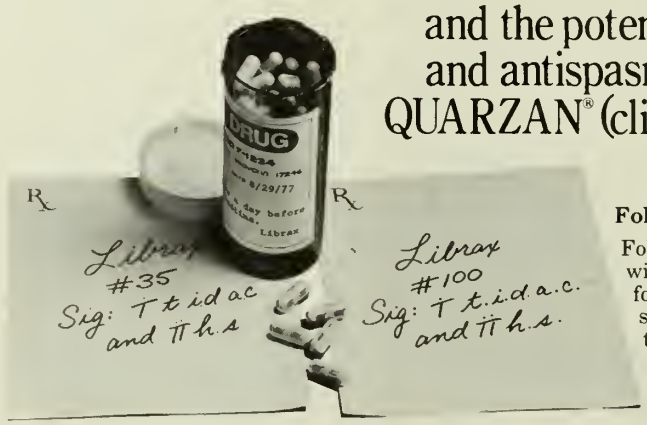

Follow-up Rx

Follow-up therapy with a prescription for a 2- to 3-week supply of medication usually helps maintain patient gains.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl/Roche) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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Microsurgical Vascular Decompression for Trigeminal Neuralgia and Hemifacial Spasm

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Vascular cross-compression of cranial nerves has been proposed as the cause of cranial neuropathies, including trigeminal neuralgia and hemifacial spasm. Over the last decade we have used microsurgical vascular decompression to treat these two disorders. Results in 50 patients treated for trigeminal neuralgia have been excellent in 42, good in 5 and poor in 2; and 1 patient was cured after a second operation. Results in 22 patients treated for hemifacial spasm have been excellent in 18, good in 2 and fair in 1. One patient died. There were no late recurrences of symptoms.

The pathophysiological mechanisms of trigeminal neuralgia and hemifacial spasm remain unknown.

GARDNER HAS REPORTED that vascular compression can cause paroxysmal hyperactive-hypoactive disorders of cranial nerves, including trigeminal neuralgia and hemifacial spasm.[1-3] Jannetta also has attributed cranial neuropathies to vascular cross-compression of cranial nerves, and has reported excellent results after microsurgical vascular decompression.[4-6] This report describes the experience between 1969 and 1979 of the senior author (C.B.W.) using microsurgical vascular decompression to treat trigeminal neuralgia in 50 patients and hemifacial spasm in 22 patients.

Patients

Trigeminal Neuralgia

Of the 50 patients treated for trigeminal neuralgia, 21 were men and 29 were women. Their ages ranged from 31 to 73 years. Pain was right-sided in 22, left-sided in 23 and bilateral in 5. Table 1 presents these data and indicates the distribution of pain and the nature of previous treatment.

Hemifacial Spasm

Of the 22 patients treated for hemifacial spasm, all but one were women. Their ages ranged from 26 to 82 years. The spasm was right-sided in 13 and left-sided in 9. Table 2 presents the clinical data on these patients.

Preoperative Management and Operative Technique

The preoperative evaluation routinely included a computerized tomographic (CT) scan and a skull series. Inasmuch as the disorder in some of the younger patients was assumed to be of vascu-

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lar origin, angiography was done to rule out the presence of a vascular malformation in these cases. In addition, angiography was carried out in all patients in whom a CT scan had shown an abnormality, such as an aneurysm or a tumor, that required further study.

Preoperative and intraoperative administration of dexamethasone, intraoperative administration of mannitol (100 grams) and mechanical hyperventilation (P_{CO_2}, 25 to 30 mm of mercury) were routine in our surgical management.

TABLE 1.—*Trigeminal Neuralgia in 50 Patients*

	Men (Total 21)	*Women (Total 29)*
Age range (and mean)	39-71 (55)	31-73 (57)
Duration of symptoms in years (and mean)	0.5-20(9.3)	0.25-20(9.4)
Lateralization of pain		
Right	8	14
Left	11	12
Both	2	3
Division		
V_1	1	1
V_2	8	7
V_3	2	8
V_{12}	0	1
V_{23}	9	10
V_{123}	2	5
Previous therapy		
Carbamazepine (Tegretol)	18	24
Phenytoin sodium (Dilantin)	14	14
Alcohol	7	8
Radiofrequency lesion	3	3
Other	3	6

TABLE 2.—*Hemifacial Spasm in 22 Patients*

	Men (Total 1)	*Women (Total 21)*
Age range (and mean)	49	26-82 (51)
Duration of symptoms in years (and mean)	15	0.4-25(6.3)
Lateralization of pain		
Right	1	12
Left		9
Previous therapy		
Carbamazepine (Tegretol)		4
Phenytoin sodium (Dilantin)		8
Other	1	4

TABLE 3.—*Abnormalities at the Trigeminal Root Entry Zone in 50 Patients*

Abnormality	*Number*
Superior cerebellar artery	32
Vein	8
Anterior inferior cerebellar artery	8
Tumor	3
Aneurysm	2
None	5

Operation in all patients was by suboccipital craniectomy, approximately 3 cm in diameter, done through a linear paramedian incision, with the patient semiprone. The details of operative exposure and microsurgical technique have been described elsewhere.[6,7] The approach to the trigeminal nerve was supracerebellar; that to the facial nerve was infracerebellar. The method used to decompress the nerve in each particular case was determined by the nature of the responsible blood vessel: veins were coagulated and divided to prevent recanalization; redundant but otherwise normal arterial loops were displaced away from the brain stem attachment of the involved nerve and prevented from migrating back into their former position by the interposition of a Teflon sponge fashioned for this purpose; and large, atherosclerotic basilar and vertebral arteries (sometimes with fusiform dilatation) that could not be displaced away from the nerves were managed by maneuvering the Teflon sponge between the vessel and the nerve at its brain stem attachment.

Three patients had tumors that were removed. In two cases the tumor (an epidermoid and a schwannoma) had displaced an arterial loop against the trigeminal nerve; the other tumor (a 10-cm meningioma) was not responsible for the patient's trigeminal neuralgia.

In five patients, no pathologic condition was evident so, by prior agreement, a selective root section was carried out.

Operative Findings

Trigeminal Neuralgia

Fifty-one operations were done on 50 patients. The vessel compressing the fifth nerve root entry zone was most commonly (32 cases) a loop of the superior cerebellar artery. Branches of the anterior inferior cerebellar artery accounted for compression in eight cases, and veins were responsible in eight. Eight patients had two vessels (either an artery and a vein or two arteries) that were considered abnormally related to the trigeminal nerve. The operative findings in all patients are summarized in Table 3.

Hemifacial Spasm

Operations were carried out in 22 patients. In 12, it was found that a branch of the anterior inferior cerebellar artery was compressing the facial nerve at its junction with the brain stem.

The vertebral artery-posterior inferior cerebellar artery complex was responsible for nerve compression in nine cases, while a vein was implicated in one case. In one case both the anterior inferior and posterior inferior arteries were implicated. One aneurysm was found; it was not expected. The operative findings in all patients are summarized in Table 4.

Results

Trigeminal Neuralgia

Results in 42 of the 50 patients have been excellent (no facial pain, no additional sensory loss and no medication required) and in 5 good (rare minor facial pain requiring no or occasional medication). One patient was relieved of pain after a second operation to decompress a vessel, the importance of which had not been recognized at the initial operation. The procedures in two patients were therapeutic failures, with severe pain recurring in both patients. One of these, the only patient addicted to narcotics, had a dramatic abnormality corrected at operation, but afterward stated that her pain was still severe. She demanded continued narcotics and did not return for follow-up visits. The other patient had no demonstrable pathologic condition, so a root section was done; afterwards, anesthesia dolorosa developed. She is unhappy with the operation and, clearly, her condition represents a poor outcome.

Follow-up in these patients ranges from four months to five years. Complications have included transient cerebrospinal fluid (CSF) rhinorrhea from opened mastoid air cells in three of our early cases, aseptic meningitis in two and partial hearing loss in one. There were no deaths. The results and complications are summarized in Tables 5 and 6, respectively.

Hemifacial Spasm

Results in 18 of the 22 patients have been excellent (no spasms and no additional weakness), in 2 good (occasional mild spasms) and in one fair (spasms persist but are less intense and far less frequent than before the operation). There was one death.

Two patients required a second operation. One of these, the first patient in the series, was not relieved by the initial operation but obtained complete relief after the procedure was carried out correctly a year later. Since that time she has been followed for nine years without recurrence of spasm. Another patient, initially relieved, had a recurrence six weeks after the operation. A second operation, at which time a sponge that had slipped was replaced, has provided complete relief for five years. Follow-up ranges from three months to ten years, averaging 2.4 years.

Complications have included partial hearing loss in three patients, transient sixth nerve palsy in two, and transient dysphagia in two. The one death was due to cerebellar hematoma caused by an acute hypertensive crisis immediately following the operation. Tables 7 and 8 summarize, respectively, the results and complications.

Discussion

This series confirms previous reports of excellent results in treating trigeminal neuralgia and hemifacial spasm by means of microsurgical vas-

TABLE 4.—*Abnormalities at the Facial Nerve Root Exit Zone in 22 Patients*

Abnormality	*Number*
Anterior inferior cerebellar artery	12
Vertebral artery-PICA complex	9
Vein	1
Tumor	0
Aneurysm	1
None	0

PICA = posterior inferior cerebellar artery

TABLE 5.—*Results of Microsurgical Vascular Decompression in 50 Patients with Trigeminal Neuralgia*

Follow-up (years)	*Number Patients*	*Pain-free (no medication)*	*Recurrence of Pain*		*No Relief*
			Mild	*Severe*	
0-0.5	10	7	3	..	..
0.5-1	5	4	1	..	..
1-2	19	17	0	2*	..
2-5	16	14	1	..	1†
TOTAL	50	42	5	2	1

*Pain-free with medication (phenytoin sodium [Dilantin]).
†Pain-free after second operation.

TABLE 6.—*Complications of Microsurgical Vascular Decompression for Trigeminal Neuralgia*

Complication	*Number*
CSF rhinorrhea	3
Asceptic meningitis	2
Sixth nerve palsy (transient)	1
Hearing loss (partial)	1
Herpes oralis	1
Repeat operation for pain	1
TOTAL	9

CSF = cerebrospinal fluid

TABLE 7—*Results of Microsurgical Vascular Decompression in 22 Patients* with Hemifacial Spasm*

Follow-up (years)	Number Patients	No Spasms (no medication)	Recurrence of Spasm		No Relief
			Mild	Severe	
0-0.5	2	2	..	..	..
0.5-1	4	3	..	1	..
1-2	7	6	1	..	..
2-5	6	5	1	..	..
5-10	2	2	..	..	..
TOTAL	21	18	2	1	0

*One additional patient died of a cerebellar hematoma immediately following the operation.

TABLE 8.—*Complications of Microsurgical Vascular Decompression for Hemifacial Spasm*

Complication	Number
Sixth nerve palsy (transient)	2
Seventh nerve palsy (transient)	2
Hearing loss (1 complete, 2 partial)	3
Dysphagia (transient)	2
Ataxia (transient)	1
Eleventh nerve palsy	1
Death (cerebellar hematoma)	1
TOTAL	12

cular decompression.[3,6,8] The procedure is safe and nondestructive, and avoids postoperative dysesthetic syndromes. The follow-up interval in our series is too short to allow the procedure to be considered curative; however, the rate of late recurrence of pain in all series has been low, there being none in the patients reported here.

The lateral decubitus position was used in this series, although others favor a sitting position. No local infarction or clinically significant air emboli were encountered. The lateral position should reduce the frequency of postoperative headache (P. J. Jannetta, MD, personal communication, April 1978), and its safety particularly recommends it for older patients.

The occurrence of CSF rhinorrhea and aseptic meningitis in this series underscores the need for scrupulously waxing mastoid air cells and preventing the entry of blood into the subarachnoid space. Postoperative cranial nerve disturbances were generally transient and may have been due to intraoperative traction. Herpetic rash occurred in only one of the 72 patients—a lower incidence than has been reported in previous series.[8] The reasons for this discrepancy are unknown. Since 1975, small amounts of Aron Alpha have been used to fix the Teflon sponge in position; and since adoption of this maneuver, it has not been necessary to reoperate as a result of slippage of a sponge.

Conclusion

Both the gradual onset of trigeminal neuralgia and hemifacial spasm in middle life or later and the reversal of functional loss by microsurgical vascular decompression are consistent with a vascular cause for these conditions; however, the pathophysiological mechanisms remain obscure. Abnormalities in myelination of cranial nerves have been observed in trigeminal neuralgia[9,10] and hemifacial spasm,[11] but their relation to vascular compression and their pathophysiological importance are unknown. Jannetta has noted that to be clinically significant, the cross-compression must be perpendicular to the nerve at the root entry zone; our empiric findings confirm this. It is at the root entry zone that central myelin is replaced by peripheral myelin. Whether conduction disturbances resulting from vascular compression are more likely at this point than elsewhere on the nerve is a matter that requires further investigation. It is not clear what the pathophysiological significance would be.

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Routine Serologic Testing for Syphilis in a Community Medical Practice

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A retrospective review of 8,100 serologic tests for syphilis ordered during a 42-month period yielded positive rapid plasma reagin test results in 127 patients (1.6 percent) and a positive fluorescent treponemal antibody absorption reaction in 91 patients (1.1 percent). Of the 36 cases of biologic false-positive reactions, most were in prenatal patients. Forty-six cases of syphilis were previously undiagnosed but antibiotic therapy was given in only 26 of the patients. Some 24 percent of syphilitic patients were not treated because the positive serologic findings were overlooked. Cerebrospinal fluid determinations were analyzed and cost-effectiveness of finding a single case of previously undiagnosed syphilis was calculated. We found that routine serologic tests and cerebrospinal fluid studies for syphilis in asymptomatic patients had low rates of positivity in our community hospital and outpatient practice.

In 1976 almost 43 million serologic tests for syphilis were done in the United States.[1] Previous studies have suggested that routine serologic tests for syphilis should be carried out more extensively in patients in hospital.[2,3] In some 6 percent of patients admitted to Buffalo General Hospital results were positive,[2] while in Grady Memorial Hospital, Atlanta, the figure was 9.5 percent.[3] The American College of Obstetricians and Gynecologists recommends that all gynecologic admissions include a routine serologic test for syphilis.[4] Most hospitals in the United States are community based.[5] Therefore, we retrospectively reviewed serologic testing for syphilis done over 42 months in a community hospital and outpatient practice.

Methods

We reviewed the results of tests for syphilis carried out from November 1974 through April 1978 in a group outpatient practice of 85 physicians and a community hospital with 150 adult medical and surgical beds. Serologic testing was initially done by the rapid plasma reagin (RPR) method. All positive RPR tests were referred to the Hawaii State Department of Health Laboratory for fluorescent treponemal antibody absorption (FTA-ABS) testing. Clinic and hospital records of patients with positive serologic findings were reviewed retrospectively to determine clinical characteristics and therapeutic outcome. Routine premarital serologic test results were excluded from analysis, because of insufficient clinical data and follow-up. To evaluate syphilis testing among individual patient groups, we also reviewed clinical records of all patients who had tests for syphilis done from January through April 1978, regardless of serologic test results. These patients' charts were evaluated for indications for ordering the tests and the rate of reactivity of each patient group (preoperative, gynecologic, and so forth). Cost-effectiveness was estimated by using a patient cost of $8.50 for an RPR test. Regardless of clinical history, a patient was considered to

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ABBREVIATIONS USED IN TEXT

BFP = biologic false-positive (reaction)
FTA-ABS = fluorescent treponemal antibody absorption
RPR = rapid plasma reagin

have syphilis if the RPR was positive and the FTA-ABS at least 1+ reactive. The serologic finding was considered to be a biologic false-positive (BFP) reaction if the RPR results were positive and the FTA-ABS negative. Also in five instances, patients with a weakly reactive FTA-ABS test were considered to have a BFP reaction, when clinical features were associated with certain underlying medical conditions.[6-9]

Results

During the 42-month study period, we reviewed results of tests for syphilis from 8,100 patients. Because many patients had preadmission tests done in the outpatient clinic, we could not accurately separate patients in hospital from those who remained outpatients. Of the 8,100 patients tested, 127 had a reactive RPR test (1.6 percent), with females comprising 54 percent of this group. Results of the FTA-ABS test indicated that 91 patients were reactive (1.1 percent of the total group). Among the 36 BFP cases, 19 were in prenatal patients; 7 were in the elderly, often among those with chronic medical conditions; 7 were in those with a collagen vascular disease, and the remainder occurred in patients for unexplained reasons. Of the 91 cases classified as syphilis, most were 2 to 4+ reactive, with only 10 patients having a 1+ reaction.

Therapeutic Outcome of Patients with a Serologic Diagnosis of Syphilis

Of the 91 patients with both positive RPR and FTA-ABS reactions, 45 patients (49 percent) had a previous history of syphilis, and of these, 35 patients (38 percent) had a history of treatment. In the latter group, 11 patients were considered to have received questionable therapy and were retreated during the study period.

The cases of the other 46 patients (51 percent of the positive cases) were previously undiagnosed. Only 26 (57 percent) of these patients received treatment. Nine patients did not receive treatment for syphilis because they had a terminal illness. For 11 patients, no reason for withholding antibiotic therapy could be determined from the records.

Of the 91 patients with syphilis, 32 underwent a lumbar puncture. Seven had elevated spinal fluid protein (range: 50 to 74 mg per dl). No spinal fluid specimen showed pleocytosis or was serologically reactive. Of the seven patients with abnormal spinal fluid protein, six had neurologic symptoms (86 percent). There was a statistically higher incidence of neurologic symptoms in patients with abnormal spinal fluid protein than in the group of 25 patients whose spinal fluid was normal (86 percent versus 32 percent; $P = .05$ by chi square analysis).

Estimated Cost and Physician Use of Serologic Testing for Syphilis

For the 42 months studied, the approximate cost of RPR serological testing was $8.50 multiplied by 8,100 patients, which equals $68,850. The cost of finding a positive case of syphilis was $68,850 divided by 91 patients, equaling $757. The cost of detecting a previously *undiagnosed* case of syphilis was $68,850 divided by 46 patients, equaling $1,497 per patient. These costs do not include the expense of the FTA-ABS tests done at the Hawaii State Department of Health Laboratories or the cost of physician services.

We reviewed the records of 830 patients who had serologic tests for syphilis ordered from January to April 1978. There were 17 patients with a positive RPR reaction (2.0 percent), and 14 patients with positive FTA-ABS test results (1.7 percent). Most of these serologic tests were ordered routinely; only 147 of the patients (18 percent) had testing done for specific indications, including neurologic symptoms, penile lesions, rash or vaginal discharge. The departments ordering the tests were as follows: medicine (477), obstetrics and gynecology (199), surgery (78), neurology (64) and dermatology (12). The rates of reactive RPR tests in these departments were as follows: medicine (1.9 percent), obstetrics and gynecology (1.0 percent), surgery (1.3 percent), neurology (6.2 percent) and dermatology (8.3 percent). The mean age of the neurologic patients with positive RPR tests was only slightly higher (48 years) than other types of patients (46 years). The reactivity rate of serologic tests ordered diagnostically was higher than for routine tests (5.4 percent versus 1.3 percent); 7 of the 17 reactive RPR tests occurred in patients with neurologic symptoms (peripheral neuropathy, optic neuropathy,

dizziness, tinnitus, vertigo, psychotic depression and transient ischemic attack).

Discussion

Our hospital and outpatient rates of positive RPR (1.6 percent) and FTA-ABS tests (1.1 percent) are considerably lower than those reported in other studies. At Grady Memorial Hospital, 9.5 percent of admitted patients had positive VDRL test results and 16.8 percent had positive findings on their FTA-ABS tests (including borderline reactions).[3] Tomecki and Plaut[2] reported that 6.2 percent of patients studied at Buffalo General Hospital had positive RPR and FTA-ABS tests. Raskind and Eisdorfer[10] in Seattle found reactivity rates of 6 percent for the VDRL (Venereal Disease Research Laboratories) test and 5.5 percent for the FTA-ABS test among elderly outpatients with dementia. Conversely, our BFP rate of 28 percent of all positive RPR tests was higher than the BFP rates found in the other studies (3 percent to 12 percent).[2,3,10] These differences in serologic reactivity of syphilis may be due to differences in patient population. Unfortunately, we are unable to compare racial status, age distribution, socioeconomic level, sexual behavior or underlying medical diseases of our patients with those of previous studies.

In this study, we attempted to estimate the cost of finding a previously undiagnosed case of syphilis. This was prompted by a report by Felman,[11] who estimated the cost of finding an early, undiagnosed case of the disease by routine premarital serologic testing in New York City to be approximately $15,000 in laboratory fees and $45,000 for physician charges. Our cost of $1,497 in laboratory fees was considerably lower because of Felman's low rate of detection of early undiagnosed syphilis (.03 percent in his population).

The clinical outcome of our patients with positive serologic findings was similar to that reported by Tomecki and Plaut.[2] In approximately half of our positive cases there had been a previous history of syphilis. Of the 46 newly diagnosed cases, 26 patients received treatment, 9 patients were not treated because of terminal illness and 11 patients (24 percent) were not treated for syphilis apparently because the positive serologic test result was overlooked. In Hawaii, private physicians, rather than the health department, have primary responsibility for patients with positive serologic findings for syphilis. We carefully examined the outpatient records of all patients with positive serologic results in our study and found that a significant percentage of these patients were lost to physician follow-up. We agree with Tomecki and Plaut[2] that there is often failure to pursue a serologic diagnosis of syphilis.

The value of examination of spinal fluid in asymptomatic patients with syphilis is controversial. The Center for Disease Control recommends spinal fluid examination for any patient with syphilis of longer than a year's duration.[12] Traviesa and co-workers[13] examined spinal fluid specimens of 30 asymptomatic patients with reactive serum FTA-ABS tests and a history of inadequate medical treatment. The only abnormal findings on examination of spinal fluid were in two patients with mildly elevated total protein. In our group of 32 spinal fluid examinations, seven patients had mildly elevated levels of total protein (highest was 74 mg per dl) with no pleocytosis and no positive spinal fluid VDRL test results. The abnormal findings in spinal fluid examinations occurred almost entirely in patients with neurologic symptomatology.

Conclusion

Whether hospitals should continue to screen for syphilis is dependent on the reactivity rate of their population, and the cost-benefit of such treatment. Certainly, however, any reactive serologic test result must be vigorously pursued, because a high percentage of these positive findings are either ignored or inadequately treated.

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Gastrointestinal Polyposis: Syndromes and Genetic Mechanisms

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Adenomas and hamartomas, two genetically transmitted histologic types of gastrointestinal polyposis, are associated in syndromes with extragastrointestinal manifestations. Adenomas that predispose to adenocarcinoma are basic to familial polyposis coli, the Gardner syndrome and the Turcot syndrome. Gastrointestinal polyps and extragastrointestinal lesions serve as a warning, providing time for diagnosis and treatment of adenomas to prevent their malignant transformation in patients and their relatives. Hamartomas with no malignancy potential, but having a tendency toward bleeding and bowel obstruction, are associated with the Peutz-Jeghers syndrome, juvenile polyposis, multiple hamartoma syndrome, basal-cell nevus syndrome and the Cronkhite-Canada syndrome. Most of these lesions and syndromes follow the inheritance pattern of a single autosomal dominant gene.

GASTROINTESTINAL POLYPS are clinically significant and experimentally useful. Some predispose to carcinoma in the colon and rectum, and others, with slight or no predisposition to cancer, cause mechanical obstruction or bleeding. The detection of precancerous polyps provides warning and time for a physician to carry out surgical operations to prevent cancer. At the same time, the accessibility of polyps affords opportunity to study their structure, genetics, cell kinetics and transformation from benign to malignant status.

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Some polyps are solitary, usually occurring sporadically, but with an increased incidence with age. One to several solitary polyps occur incidentally in about 10 percent of adults. Polyposis refers to multiple polyps—for our purposes, 100 or more. The most common form of polyposis is adenomatosis of the colon and rectum (ACR). This condition is clinically important because of the strong association between colorectal polyposis and adenocarcinoma. Familial polyposis coli (FPC) is rare and generally occurs in combination with other abnormal growths as part of a syndrome. Polyposis coli is the predominant and most important feature of the Gardner syndrome (GS). Gastrointestinal hamartomas, though less common than adenomas, also occur individually or multiply as part of a polyposis syndrome. Hamartomas are not strongly associated with carcinoma

ABBREVIATIONS USED IN TEXT

ACR = adenomatosis of the colon and rectum
FPC = familial polyposis coli
GS = Gardner syndrome

but may cause obstruction or bleeding. Intestinal hamartomas occur in the Peutz-Jeghers syndrome and in juvenile polyposis coli (Figure 1). Other less common but clinically and histologically distinct polyposis syndromes are on record (Table 1). Each presents unique problems of possible genetic mechanisms, and of accurate diagnosis and management.

Herein we review the progress that has been made in understanding the various gastrointestinal polyposis syndromes; examine the relationship of polyps with other manifestations of these syndromes; and describe genetic mechanisms as well as methods for early detection and management to prevent the development of malignant lesions.

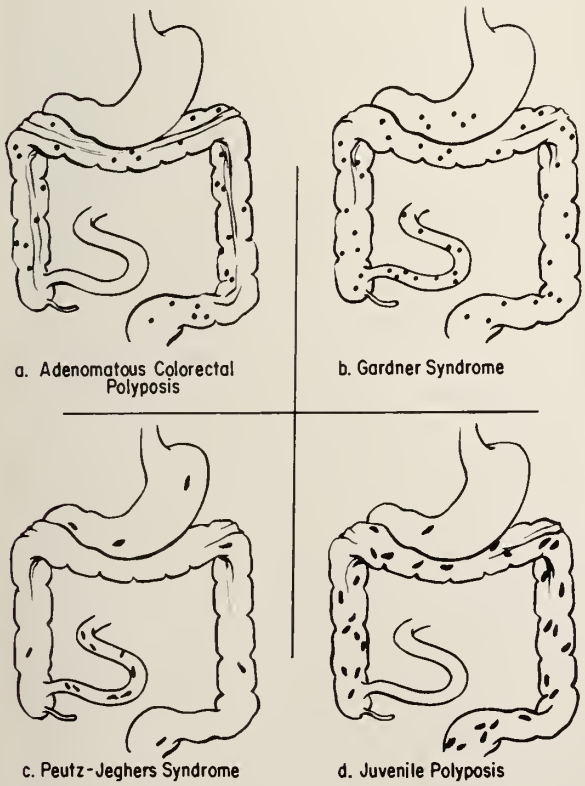

Figure 1.—Schematic representation of the distribution, number and size of polyps in the major *adenomatous* polyposis syndromes, (a) adenomatous rectal polyposis and (b) the Gardner syndrome, and the major *hamartomatous* polyposis syndromes, (c) Peutz-Jeghers syndrome and (d) juvenile polyposis.

TABLE 1.—*Gastrointestinal Polyposis Syndromes*

Syndrome	*Histology*	*Distribution*	*Malignant Potential*	*Other Manifestations*	*Genetic Mechanism*
Familial polyposis	150 to 5,000 adenomas	Colorectum	High	None, but included in many syndromes	Autosomal dominant
Gardner syndrome	25 to 200 scattered adenomas	Colorectum, occasionally esophagus, stomach, small bowel	High	Osteomas, epidermoid cysts, fibromas, desmoid tumors, mesenteric fibromatosis, dental abnormalities	Autosomal dominant
Turcot syndrome	Scattered adenomas	Colorectum	High	Central nervous system tumors	Autosomal recessive
Familial discrete polyps	1 to 6 scattered adenomas	Colorectum	High	None	Autosomal dominant
Peutz-Jeghers syndrome	Hamartomas	Entire GI tract, mainly stomach, small bowel, colorectum	Low or absent	Pigmentation of lips and skin	Autosomal dominant
Juvenile polyposis	Most hamartomas, few adenomas	Entire GI tract, most common in colorectum	Low	Anemia, protein-losing enteropathy	Some familial
Multiple hamartoma syndrome (Cowden disease)	Multiple hamartomas	Gastrointestinal tract	None	Warty papules on mucosa and skin, multiple malformations	Autosomal dominant
Basal cell nevus syndrome	Multiple hamartomas	Stomach (see text)	None from GI polyps (skin cancer)	Benign mesenteric cysts	Autosomal dominant
Cronkhite-Canada syndrome	Thickened mucosa, likened to juvenile polyps	Stomach, small bowel, colon	None	Skin pigmentation, nail atrophy, alopecia, protein-losing enteropathy	All cases sporadic, probably nongenetic

GI = gastrointestinal tract

Much of the information is based on data from continuing studies of patients with familial polyposis coli and from reports on the original kindreds of the Gardner syndrome. This study was initiated by one of the authors (E.J.G.) more than 30 years ago.

Familial Polyposis Coli

Although single cases of probable adenomatous polyposis were reported as early as 1861 and 1873,[1] Cripps[2] in 1882 first recognized the hereditary nature of the disease. In 1887 Smith[3] stressed the familial concept and noted early development of malignant lesions in FPC patients as did Handford in 1890.[4] Lockhart-Mummery[5,6] clearly established the genetic background of colonic polyposis, emphasizing the autosomal dominant mode of inheritance. Reviews of FPC by Dukes[7-9] in 1930, 1952 and 1958 were based on his own extensive family history studies and the pedigree records at St. Mark's Hospital in London, a specialty hospital established in 1835 and dedicated to research and treatment of bowel diseases. Guptill[10] reviewed the FPC literature to 1947, Veale[1] recorded his research and extended the literature review up to 1965 and Bussey furthered the research phase in his study in 1975.[11] Erbe[12] described polyposis syndromes and Rawson[13] summarized the relation of colonic polyps to large bowel cancer in 1976. FPC was further explored by Sachatelle and colleagues.[14,15] Medical and surgical measures to prevent colon cancer were reviewed by DeCosse and associates in two different reports in 1977.[16,17] Schuchardt and Ponsky[18] recently evaluated the Gardner syndrome in relation to FPC. The contribution of these authors and others has led to a better understanding of the histopathology, cell kinetics and natural history of FPC.

Cancer may develop in one or more of the adenomas. On the average, 15 years are required for transformation of an adenoma to an adenocarcinoma. However, even before malignant transformation, multiple polyposis may cause significant symptoms such as abdominal pain, diarrhea, blood-stained stools, loss of weight and anemia.

Most FPC polyps are pedunculated adenomas which hang on stocks of mucosa that are continuous with the inner lining of the intestine. But others, such as villous adenomas, are sessile and different in structure. They arise from the mucosa on a broad base. Villous adenomas are initially dome-like above the mucosal surface but later become separated into finger-like processes consisting of thin strands of stroma covered by epithelium. Generally, they are isolated, and occur most frequently in the rectum and sigmoid colon. Villous adenomas become larger than pedunculated adenomas, some reaching 15 cm in diameter, and have been known to become cancerous.

Most FPC adenomas are hyperplastic and provide suitable material for studies of cell kinetics. Adenoma cells undergo excessive cell division as they migrate upward from the base to the surface of the colonic mucosa. In contrast, dividing cells from normal colonic mucosa are seen only in the lower levels of the mucosa.[19] As the cells migrate toward the surface, division ceases and the cells differentiate to become flat as they line the intestine. In the presence of the FPC gene, DNA synthesis is not depressed and cell division continues as clusters of dividing cells migrate to the surface. These clusters are presumed to represent the origin of adenomas. Lipkin[20,21] and Deschner and Lipkin[22] traced labeled (3HTdR) colonic cells from patients with FPC. The cells exhibited continuous proliferation as they passed the mid-level of the crypts of Lieberkühn and on to the mucosal surface.

The treatment of choice is colectomy, but the extent of the resection and its timing are based more on empiricism than on fact. A subtotal colectomy with an ileorectal anastomosis is generally carried out in young patients to avoid the possible adverse social and emotional consequences of ileostomy. They must be evaluated periodically for the detection and removal of adenomas in residual colorectal tissue. Unfortunately, the optimum frequency at which evaluations should be done has not been established. The continuing concern with the risk of cancer and the decreasing concern with the consequences of ileostomy may lead to resection of residual rectum. Some surgeons[23] consider the risk too great if any part of the large bowel is not removed. They insist on total colectomy and ileostomy. However, data are inadequate at present to settle this issue.[24] Nevertheless, any patient who undergoes a subtotal colectomy should be fully informed of the need for long-term follow-up and the possibility that eventually a second operation may be necessary. Conversely, those who carry out total colorectal resection should make available to the patient the extensive resources and

technology that can minimize the inconvenience and psychosocial consequences of ileostomy.

The Gardner Syndrome

Thirty kindreds have been classified as FPC in studies of cancer in Utah families initiated by Stevens, Gardner and Woolf in 1947. Kindreds 109[25,26] and 134[27] were found to have common extracolorectal lesions in addition to multiple adenomas of the colon and rectum. These persons were eventually designated as having the Gardner syndrome.[28]

The Kindred 109 Study

Kindred 109 (Figure 2), from which the syndrome was described, became a part of the study in 1947. A University of Utah premedical student, Eugene Robertson, in a genetics class called attention to a neighbor family in his hometown that had a high incidence of colon cancer. Family members were cooperative in a clinical investigation that has continued for more than 30 years. Before the study was initiated, eight deaths among family members had occurred from colon carcinoma.[28] Initial examinations of the 51 living descendants of the progenitor, in whom the first case of colorectal adenomas had occurred, disclosed six cases of intestinal polyposis. Adenocarcinoma was already present in two of the six. All six patients underwent colectomies. Five recovered and were apparently cured of colorectal adenomatosis and the threat of carcinoma. The sixth patient, a 45-year-old man with widespread carcinoma at the time of the first examination, died of complications following a surgical operation.[28] Another of the six patients died at the age of 22, three years after colectomy, of inoperable mesenteric fibromatosis and small bowel obstruction.

The ages of the six patients ranged from 13 to 44 years at the time of the first examination or the onset of symptoms. The 13-year-old boy was entirely free of adenomas when first examined by sigmoidoscopy and barium enema at 11 and 12

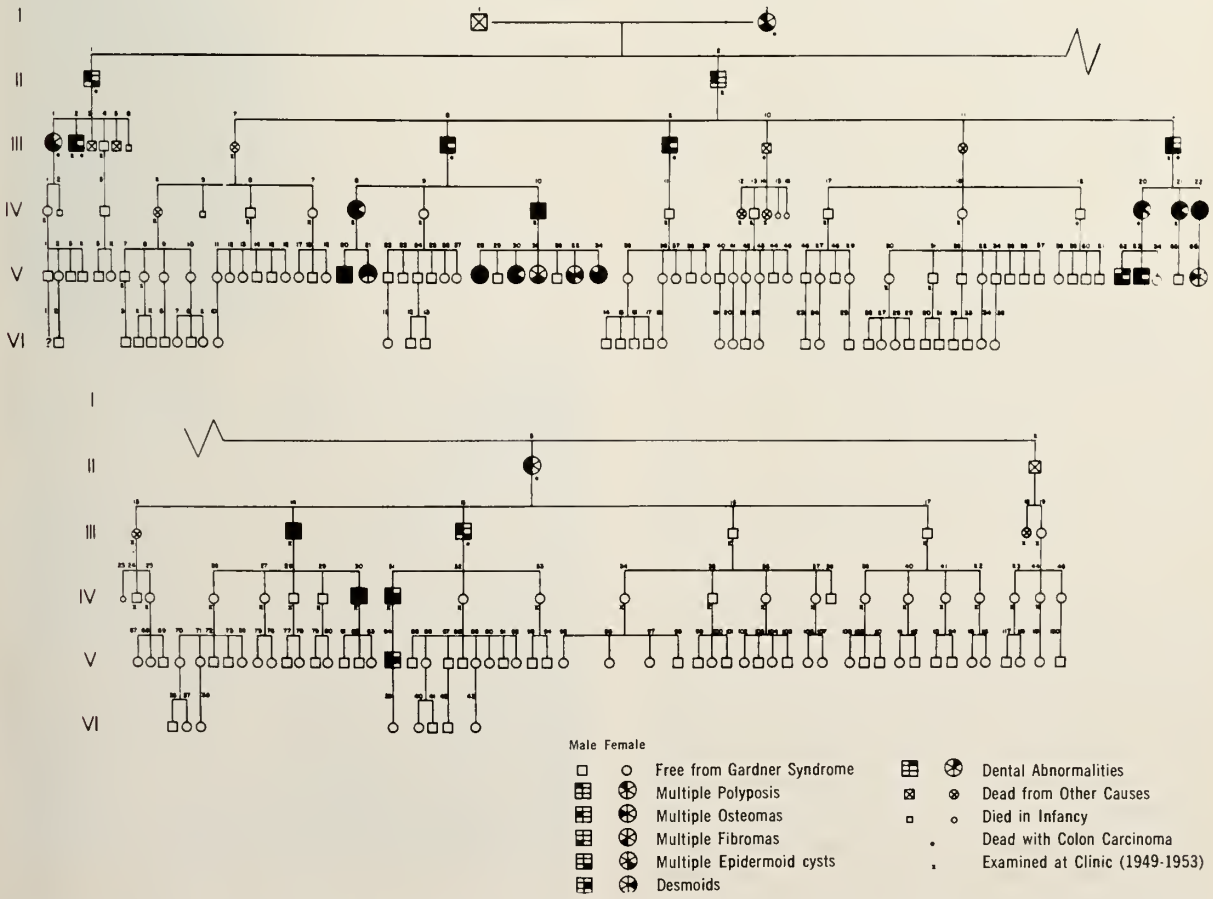

Figure 2.—Pedigree of kindred 109 showing the manifestations of the Gardner syndrome documented thus far in five generations. The portion of the pedigree in the lower half is an extension of the second generation and those that follow.

years of age. At age 13, one minute adenomatous polyp was seen 11 cm above the anus. Examinations at intervals of about six months over four years showed increasing numbers of polyps spreading over the entire colon and rectum. A subtotal colectomy with ileorectal anastomosis was carried out when he was 18. Some 75 adenomas, widely distributed throughout the colon, were present in the specimen. Polyps have been removed from the rectum at three-month intervals since the ileorectal anastomosis. The number of rectal polyps noted has remained fairly constant over the last 25 years, ranging from 0 to 20 at each three-month interval.

Among the 51 descendants of the female progenitor, 45 had no adenomas at the time of the initial survey. Relatives in other branches of the related kindred were examined. No adenomas were found except among the descendants of the original patient who died of carcinoma of the colon in 1909. It was therefore postulated that a mutation had occurred in this woman.[29] In 1950 adenomatosis of the colon and rectum in kindred 109 was under control, the retrospective study of FPC was completed and a prospective investigation was well under way. Extracolorectal lesions were observed in kindred members which led to further study of the condition that later became known as the Gardner syndrome.

In examining the 51 family members for intestinal polyps, "bone tumors" as well as cutaneous and subcutaneous growths were detected in some of the patients with ACR. The six family members found to have colorectal adenomas also had multiple osteomas of the skull and of the arm and leg bones. In addition, two children aged 7 and 11 had multiple osteomas.[30,31]

Soft cutaneous growths, found to be epidermoid cysts, were next described[32] in the same patients. Seventeen large cysts ranging in size from 3 to 8 cm were counted in a 36-year-old patient during an initial examination. He also had 12 smaller cysts and about 24 scars from previous excisions of cysts. His two daughters aged 2 and 4 had many small (3 to 5 mm) cysts in continuous masses over their upper chests, backs, shoulders and upper arms, as well as 6 and 12 cysts, respectively, on their faces. Subcutaneous fibromas were then detected in all six patients previously found to have multiple adenomas and osteomas. The fibromas ranged in size from 5 mm to 3 cm and occurred on the scalp, shoulders, arms and back.[29] These three extracolorectal growth abnormalities, osteomas, epidermoid cysts and subcutaneous fibromas, in addition to the multiple adenomas formed the basis for the syndrome that was named the Gardner syndrome by Smith in 1958.[33]

In 1962 Fader and co-workers[34] added abnormal dental features—unerupted and supernumerary teeth—to the syndrome. These dental abnormalities along with odontomas were soon found in members of kindred 109. Excessive dental caries and distinctive facies that were observed in kindred 109 were considered at one time to be related to the syndrome; however, these have since been found to be either secondary to osteomas and other abnormalities or attributable to other causes.

Desmoid Tumors

Smith[35] reported in 1959 that desmoid tumors occurred more frequently in patients with multiple adenomas than in the general population. Pack and Ehrlich[36] reported that between 1917 and 1943, only 17 desmoid tumors of the abdominal wall were encountered among 50,346 cases of neoplastic disease at the New York Memorial Hospital, for a gross hospital incidence of 0.03 percent. Dahn and colleagues[37] found only 33 cases diagnosed at the Institute of Pathology in Lund, Sweden, from 1945 to 1959, and estimated the incidence in the general population to be two cases per year per million population. However, Smith[35] found seven cases in a series of 201 patients with FPC for an incidence of 3.5 percent. This was considerably higher than the incidence of desmoid tumors complicating any other known disease or abdominal operation in an unselected series of cases.

Shiffman[38] in 1962 surveyed 90 cases of GS in the literature and found desmoid tumors reported in 17 percent. One large desmoid tumor removed at the Mayo Clinic by Simpson and coworkers[39] measured 30 cm by 30 cm by 15 cm. These investigators also cited fibrous masses not organized into definite tumors but described as "diffuse fibrous infiltration." Jones and Cornell[40] reported desmoid tumors in 13 of 75 patients with the syndrome, for an incidence of 17.3 percent. In the living members of the original GS family, 38 percent with the syndrome have been observed to have either desmoid tumors or locally invasive mesenteric fibromatosis. This is an underestimate for desmoid potential in kindred 109, because nine members died between the ages of

28 and 58, most without having had surgical operations and five children without desmoid tumors have not yet had operations.

Classically, desmoid lesions have been considered to be tumors of the anterior abdominal wall that develop as a result of trauma. Generally, they develop within incisions after operations.[41] In 1923 Nichols[42] reported desmoid tumors in locations other than the abdominal wall. It has since been recognized that desmoid lesions can appear in musculoaponeurotic structures throughout the body.[43,44] In three patients in kindred 109, spontaneous desmoid tumors developed without previous surgical injury. All three patients were girls. In one a lesion of the left upper anterior abdominal wall was noted at birth, in another a posterior left chest lesion was discovered at 8 months of age, and in the third a gluteal tumor was found at 11 years of age. Shepherd[45] and Karakousis and co-workers[46] reported the occurrence of mesenteric or retroperitoneal fibromata in patients with FPC who had previously undergone colectomy. Shepherd[45] also noted that the most common site of occurrence was in the base of the small bowel mesentery. Among the 11 cases of desmoid tumors and mesenteric fibromatosis now recorded in kindred 109, six were associated with postsurgical scars and five with no previous operations or known trauma.

Figure 3.—Roentgenogram showing osteomas in forearm and foreleg bones of a patient with the Gardner syndrome.

Figure 4.—Roentgenographic appearance of the maxilla and mandible of a patient with the Gardner syndrome showing numerous supernumerary and unerupted teeth.

Desmoid lesions are nonmetastasizing, locally invasive benign fibrous tumors that are clearly related to fibromas and fibrosarcomas; however, their differences need to be stressed. Fibromas are more superficial, smaller, encapsulated and noninvasive, and after excision usually do not recur in the same place. Fibrosarcomas are more apt to be pseudoencapsulated and softer, to have a homogeneous salmon-pink color and to arise without a previous history of injury. Microscopically, a fibrosarcoma is more cellular, undergoes more mitoses and frequently shows abnormal mitotic figures. Metastatic lesions are generally seen in patients with fibrosarcomas but have never been described in desmoid tumors.

Extracolorectal Lesions Previously Associated With Gastrointestinal Adenomas

In 1912 Devic and Bussy[47] reported the case of a woman who died of cancer of the intestines:

> She also had many lipomas on her leg, sebaceous cysts on the head, a tumor on the back of her neck as big as a walnut, a small goiter, four osteomas of the lower jaw, dozens of small fibro-lipomas and many larger ones, and one very large tumor in the intestines, and adenoma of the kidneys.

McKittrick and associates[48] in 1935 described a patient with gastrointestinal lesions and multiple extracolorectal disorders. Miller and Sweet[49] in 1937 recorded the first instance of extracolonic findings in a patient diagnosed as having familial polyposis. Veale[1] recorded 17 cases of extracolorectal neoplastic lesions in FPC families seen at St. Mark's Hospital in London. The numerous and varied examples of extracolonic lesions now on record are said[18,50] to form a continuum from the classic FPC families in whom no extracolonic manifestations are seen to the most extreme cases, such as the one described by Devic and Bussy.[47]

Gardner's kindreds 109[26] and 134,[27] once considered examples of FPC, now include members with osteomas (Figure 3), dental abnormalities (Figure 4), epidermoid cysts, benign fibromas (Figure 5), desmoid tumors and mesenteric fibrosis along with multiple adenomas. Pierce and co-workers[51] described a large Canadian kindred first as FPC and later as GS. The St. Mark's group with some 230 families accumulated and studied for many years now lists some 50 families with at least one member expressing one or more features of GS, and 20 families containing between two and nine persons with some features of the syndrome. Among the more than 200 families under investigation by A. J. Krush, MS, investigator of FPC families at Johns Hopkins University (written communication, 1979), 37 are classified as having GS compared with 21 with FPC. Many patients and families with FPC and extracolorectal lesions described previously would now be classified as having the Gardner syndrome.

Other lesions associated with colorectal adenomatous polyposis include malignant tumors of the central nervous system (Turcot syndrome),[52] periampullary malignant lesions and adenocarcinoma of the duodenum,[53-57] cancer of the urinary bladder,[57] thyroid,[58] gallbladder,[59] fibromatosis of the breast[60] and lesions of the upper gastrointestinal tract.[61,62] These are not included generally as parts of the Gardner syndrome, and most appear to be coincidental. In spite of the number of FPC families eventually found by careful scrutiny to have GS stigmata and other lesions, the great majority of FPC families studied at St. Mark's[11] and elsewhere have no more than the number of extracolonic lesions expected in general populations. Kindred 269, with several hundred members and some 30 cases of FPC, has been investigated by Gardner and associates since 1964 and has shown no evidence of GS.

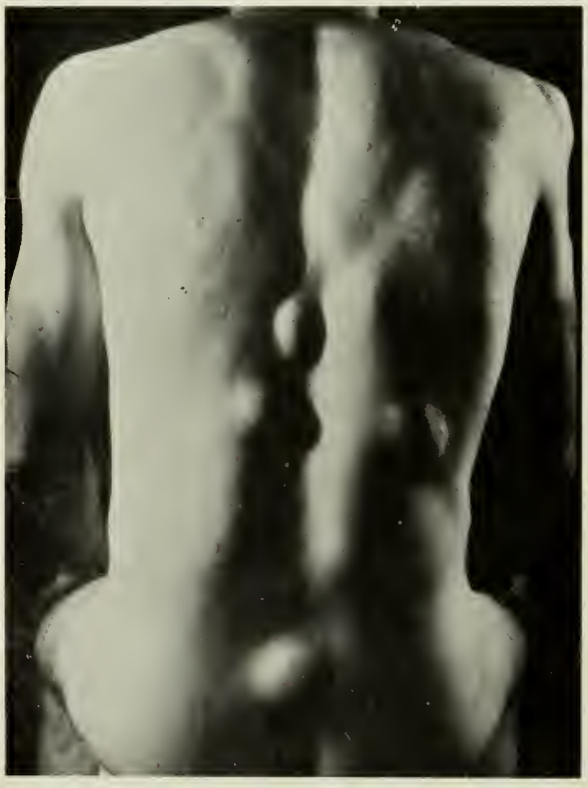

Figure 5.—Large epidermoid cysts in a patient with the Gardner syndrome. Subcutaneous lesions were also present on the arms, face and shoulders.

Similarities and Differences Between FPC and GS Polyps

Differences listed over the years to distinguish between adenomas of FPC and of GS have diminished. Adenomas from both sources seem to be histologically, pathologically, developmentally and genetically similar.[1,11,16,18] The great variation in age of onset, number and location of polyps applies to both entities.[11,18] In kindred 109 all 17 thoroughly examined affected members presented with the first colorectal polyp between the ages of 11 and 18. Naylor and Lebenthal[63] reported a member of a GS kindred in whom polyposis was detected at 18 months of age. Bussey[11] found from the St. Mark's Hospital Polyposis Register that children as young as 4 years old had FPC polyps. At the other end of the spectrum, great variation exists in age at first observation, but only data from people examined before and after onset are valid for evaluating late diagnosis. Bussey lists the oldest at 72 years. For diagnosis of adenomatosis in the propositus group, Bussey listed the mean age as 35.8 years. A careful comparison to establish age of actual late onset has not been done.

In kindred 109, there are 24 of the 29 members with the syndrome who now have colorectal adenomas. The remaining five are younger than 14 years of age and are under observation for onset of colorectal adenomas. Watne and co-workers[64] found colon polyposis in 67 percent of their 126 patients with GS.

The number of polyps in individual patients is age-related and any comparison must include age as well as other factors. Each person carrying the FPC or GS gene will have a single polyp or a very few at the onset of the disease. As the patient

grows older, at least through the teen years, polyps increase in number and size. Bussey[11] found up to 5,000 polyps in some FPC patients. The average is about 1,000, with a usual range of from 300 to 3,000 (see Figures 6 and 7). The lowest figure recorded in the St. Mark's Hospital series was 150 polyps.[11] In contrast, only a few of living affected members of kindred 109 who have been observed during the past 30 years have had 100 polyps and none has exceeded 200 (Figure 8).

Figure 6.—Barium contrast roentgenogram of a patient with familial polyposis showing hundreds of polyps.

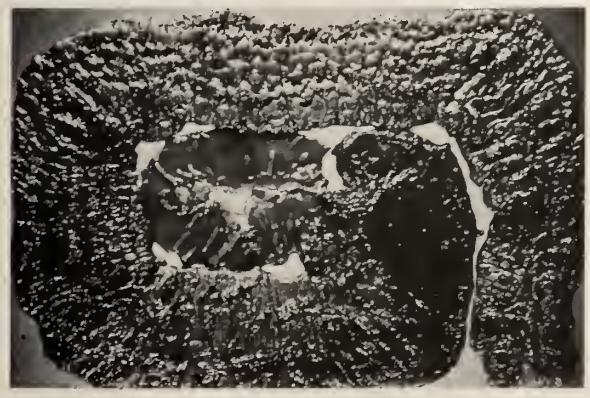

Figure 7.—Gross appearance of colon resected from a patient with familial polyposis showing a carpeting of the colon with a continuum of polyps. Over 1,000 polyps are present.

Surgical intervention has prevented the development of large numbers of polyps in patients treated more recently. But based on results of examination of colon specimens at colectomy, it is difficult to imagine tremendous numbers of polyps developing at any age in untreated persons with Gardner syndrome before they die of colorectal carcinoma. McKusick[65] has suggested that polyps are fewer, larger and more widely scattered in GS patients as compared with a more continuous carpeting of small polyps in FPC patients. Observations in Utah family studies and those of DeCosse and associates[66] support McKusick on these points. However, the more distinctive features of GS are the extracolorectal lesions.[28,67,68]

Early Diagnosis and Identification of High-Risk Persons

Early diagnosis[69-71] and identification of high-risk persons[72,73] for adenomas and adenocarcinoma of the colorectum are the subjects of major research efforts. However, no single, reliable method has been developed as yet from these investigations. In a study of patients with hereditary polyposis, colonoscopy was found to be the most accurate method for identifying adenomas in the colon and rectum in high-risk persons; barium enema and fecal occult blood determinations were regarded as supportive measures.[74] Growth characteristics of fibroblasts in culture[75] are being studied as possible markers in the detection of asymptomatic carriers of a multiple adenomatosis gene. Osteomas in the mandible and

Figure 8.—Gross appearance of colon resected from a patient with the Gardner syndrome showing multiple scattered polyps throughout the colon.

maxilla[30,76] can be detected in some patients with GS before colon polyps appear. Tetraploidy or aneuploidy[77-79] in cultured epithelial cells may provide a marker for adenomatosis, at least at the time when polyps are in the colorectum. Studies to evaluate the usefulness of this marker as a diagnostic measure are in the developmental stage. Current investigations on cell kinetics in the origin of adenomas[20-22] give promise of markers for the diagnosis of polyposis coli before the polyps actually appear.

Other Adenomatous Polyp Associations

Rare cases of adenomatous polyps have been associated in particular families with tumors in the central nervous system. This combination has been called the Turcot syndrome.[52,80] Another grouping of a few scattered adenomas of the colorectum but without extracolorectal manifestations has been postulated to follow an autosomal dominant pattern of inheritance.[81] Twenty-five (45 percent) of the members of kindred 133 (all in one generation) had occasional discrete polyps of the colorectum compared with one questionable polyp in the control series of 21 spouses of the individual persons examined. Kindred 133 had a history of excessive carcinoma of the gastrointestinal tract.[82] Members of families with this condition—that is, the occurrence of occasional discrete polyps of the colon and rectum—are under reinvestigation at present.

Genetic Mechanisms

The entire phenotype for FPC and the most constant and basic aspect of GS is the dominantly inherited multiple adenomatosis of the colon and rectum. This is also the most clinically significant part of the Gardner syndrome because of the inevitable transformation from benign adenomas to colorectal adenocarcinomas. In hereditary pattern, pathology and natural history, FPC and GS adenomas are apparently identical. The same basic gene *P* or an allele of *P* is postulated to control the origin of adenomas in both disease entities.

Genes *Pp* are postulated for advanced adenomatosis at an early age, *P*+ for only a few adenomas usually occurring after the third decade of life, and *p*+ and + + for people free from inherited colorectal adenomas.[1,83] Because of the very low frequency of *P*, the genotype *PP* seldom, if ever, occurs. The recessive *pp* genotype was postulated[1] for a few discrete polyps as described by Smith and Kern.[50]

The intriguing problem is the number of genetic entities in the multiple adenoma complex. Single dominant genes are known to give rise to great phenotypic heterogeneity. Gene *P*, controlling or depressing a genetic system for a generalized growth promoter could account basically for colon adenomas and abnormal growth in a wide spectrum of susceptible tissues. This would explain the single continuum of ACR alone and in combination with extracolorectal lesions as postulated by Sachatelle,[14,15] and Smith and Kern.[50] McKusick,[65] on the other hand, has suggested separate genetic status for FPC and GS, and others[16] support this position. Both explanations invoke differences in penetrance, expressivity and unspecified modifiers to explain the observation of wide phenotypic variation. But these terms only make ignorance respectable. The proportion of persons carrying a given dominant gene that expresses the phenotype (penetrance) and the degree of expression in different persons carrying the same gene (expressivity) must ultimately be explained by genetic, environmental or enzymatic factors. An explanation of mechanisms is made easier by inclusion of a second *P* allele (P^G), here postulated and remaining for experimental confirmation or rejection.

On the premise that FPC remains phenotypically and genetically distinct from GS, an allele of *P* (P^G, with *G* superscript for growth factor) is proposed. A gene-controlled growth factor such as the nerve-growth factor in the serum of patients with von Recklinghausen neurofibromatosis,[84] the epithelial-growth factor found in salivary glands of male mice,[85] or the connective-tissue growth factor in connective tissue tumors,[86] but more generalized, could account for colorectal adenomas and extracolorectal lesions in the same people. Genes P^Gp may control the strong expression of GS as shown in kindred 109, and P^G+ the weak expression, such as that shown in the families of the St. Mark's Hospital series having one or two of the extracolorectal stigmata of GS. Veale[1] has estimated that the incidence of the *p* allele in the British population is high, approaching 0.5. However, genotypes P^GP^G and P^GP would occur infrequently, if at all.

Hamartomatous Polyposis

Hamartomatous polyps are malformations of connective tissue of the intestinal mucosa that

have undergone excessive growth. They occur as large solitary tumors or as multiple growths that continue to enlarge. They have little or no precancerous potential, although they may cause bowel obstruction. Also, as they mature, ulceration and bleeding may result in anemia. These polyps occur in the Peutz-Jeghers syndrome, juvenile polyposis, multiple hamartoma syndrome, basal-cell nevus syndrome and the Cronkhite-Canada syndrome.

Peutz-Jeghers Syndrome

This syndrome consists of hamartomatous gastrointestinal polyps and spotty melanin pigmentation of the lips, buccal mucosa, palms and soles. The pigmentation occasionally occurs on the face, dorsal surface of fingers, toes and other parts of the body. One of Peutz's patients[87] had pigmentation of rectal mucosa at the age of 4. The black or brown patches on the lips and buccal mucosa usually measure from 1 to 5 mm in diameter. The pigment appears at birth or within two years of life and becomes less visible by the time patients are 25 years of age and older.

Hamartomatous polyps may occur in any part of the gastrointestinal tract in patients with the Peutz-Jeghers syndrome, but the presence of polyps in the small intestine is the constant feature of the syndrome. The few cases of gastrointestinal carcinoma that have occurred in patients with the Peutz-Jeghers syndrome are not due to the hamartomatous polyps. Adenomas also present in some cases may be involved in the transformation to cancerous lesions. Most cases of carcinoma of the stomach and small intestine have occurred in patients younger than 40 years old—the "cancer age" of those with other syndromes in which adenomas transform to adenocarcinoma.

In the group of ten cases followed by Jeghers and co-workers,[88] six involved more than one member of the same family. Data from these families and others showed a single autosomal dominant gene inheritance pattern.

Juvenile Polyposis

Juvenile polyposis is a rare disease that usually occurs in the first decade of life; however, in some cases, juvenile-type polyps occur in adults. The intestinal tumors are mostly hamartomas,[89] although adenomas may also be present. These polyps, like Peutz-Jeghers hamartomas, may occur anywhere in the gastrointestinal tract, but they are found most often in the colon and rectum. They appear in greatest number in the rectum, less frequently in the sigmoid area, and are found even less often in other regions of the colon.[1] They contain abundant stroma of connective tissue and cystic glands lined by goblet cells. Each tumor eventually ulcerates and bleeds. Some 50 cases of juvenile polyposis encountered in 36 families are recorded in the St. Mark's Hospital Polyposis Register.[83] In three fourths of these families, only one affected member is known and in a fourth, two to five members have polyposis, suggesting a genetic origin, at least for the familial group. The more numerous single cases may result from environmental factors, or they may arise from new mutations. These hamartomas have no potential for malignant transformation. The few cases of intestinal cancer may be attributed to the tract. Definitive information regarding inheritance and malignant transformation awaits results of further studies involving more cases.

Multiple Hamartoma Syndrome (Cowden Disease)

In 1963 Lloyd and Dennis[90] described an unusual symptom complex including tumors in several parts of the body. The entity was called Cowden disease, based on the family name of the propositus. Nine years later Weary and colleagues[91] reported five cases of this syndrome and noted gastrointestinal tumors are one of the stigmata. They found the disorder to consist of a complex mixture of ectodermal, mesodermal and endodermal hamartomatous lesions. Multiple hamartoma syndrome was proposed as a more precise name for the disorder.

The multiple hamartomas that occur in familial patterns through several generations[92] are also associated with a remarkable array of other abnormalities. These include characteristic warty papules and nodules on mucosal and cutaneous surfaces of the mouth, face, forearms and hands of young adults. These surface markers, besides signaling the presence of gastrointestinal hamartomatous polyposis, may also indicate the presence of other combinations of fibrocystic breast disease, thyroid adenomas, adenoid facies, mandibular and maxillary hypoplasia, scoliosis, fibromas, angiomas, lipomas, high-arched palate, microstomia, liver and bone lesions, nervous system abnormalities and other widely distributed malformations.[93] The syndrome is inherited in an autosomal dominant pattern. Japanese investiga-

tors[94] have reported a case of atrial myxoma associated with multiple hamartomas, supporting a theory that implicates hamartoma with the origin of cardiac myxoma. The condition is very rare.

Basal-Cell Nevus Syndrome and Gastrointestinal Polyposis

A patient with the hereditary basal-cell nevus syndrome underwent a surgical operation for ovarian fibromas at Massachusetts General Hospital in 1976.[97] Unfortunately, the status of the gastrointestinal tract was not described. In the Roswell Park Memorial Institute records for 1974 to 1975, a 54-year-old man with the basal-cell nevus syndrome was reported to have multiple hamartomatous polyps of the stomach and a benign mesenteric cyst.[96] We are not aware of other reports that document the association between the hereditary basal-cell nevus syndrome and gastrointestinal hamartomatous polyps. However, since gastrointestinal evaluations are not ordinarily done on basal-cell nevus patients, a possible association could be overlooked.[96]

Cronkhite-Canada Syndrome

The Cronkhite-Canada syndrome[97] consists of polyposis of the stomach, small intestine and colon. The polyps are thickened areas of mucosa similar to juvenile polyps.[16] Virtually the entire gastrointestinal mucosa was replaced by polypoid lesions in the cases originally reported.[97] Associated lesions include ectodermal defects such as nail atrophy, alopecia, excessive skin pigmentation and hypoproteinemia. This syndrome is very rare; only four cases have been reported.

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Craniosynostosis and Craniofacial Anomalies

KENNETH LYONS JONES, MD:* In most instances, craniosynostosis occurs as an isolated defect in otherwise completely normal children. However, sutural synostosis may represent only one abnormal feature in a multiple malformation syndrome. To provide appropriate prognosis and counseling on risk of recurrence, an accurate diagnosis must be made. Therefore, a practical approach to the evaluation of children with this condition is essential (Figure 1).

Classification of Craniosynostosis

When evaluating children with craniosynostosis, it is important first to make a distinction between primary craniosynostosis, which is due to an alteration in sutural growth, and secondary craniosynostosis, which is due to an impairment in the growth of the brain. In the latter situation the sutures fuse because they are not pushed apart by the brain's growth. The importance of making this distinction relates to prognosis. Children who have secondary craniosynostosis are, for the most part, severely impaired neurologically. They have a poor prognosis for intellectual development, and they do not benefit from surgical procedures that have been developed recently. Conversely, in most cases, children with primary craniosynostosis are normal neurologically, and their prognosis for intellectual development is very good. They are the best candidates for surgical operations because they have potentially normal brains which should grow properly following surgical correction.

Further classification of primary and secondary forms of craniosynostosis, as depicted in Figure 1, can be helpful in reaching a specific diagnosis, which is imperative for determining accurate prognosis and risk of recurrence. Primary craniosynostosis may represent a single primary defect in an otherwise normal child, or it may be one feature of a syndrome involving multiple malformations. Most cases involving a single primary defect are sporadic, representing isolated events in otherwise healthy families. Less frequently, primary craniosynostosis may be due to a single gene, in which instance the recurrence risk can be 0 percent, 25 percent or 50 percent, depending on whether it represents a fresh gene mutation, an autosomal recessive disorder or an autosomal dominant disorder in which one of the parents is similarly affected.

Primary craniosynostosis may also be seen as a feature of a multiple malformation syndrome. Table 1 lists multiple malformation syndromes known to be associated with craniosynostosis, a subject recently reviewed by Cohen.[1] Three of the disorders are due to abnormal chromosomes,[2-4] nine are disorders secondary to a single gene,[5-8] and one is secondary to a teratogen.[9] In addition, there are three multiple malformation syndromes for which causes remain unknown.[10-12] Of all of the disorders listed, the Crouzon syndrome (craniosynostosis, maxillary hypoplasia

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and shallow orbits) and the Apert syndrome (craniosynostosis, midfacial hypoplasia, and syndactyly) are the most common. Both of these conditions are genetically determined disorders with an autosomal dominant mode of inheritance.

Secondary craniosynostosis is sometimes the result of a single primary defect (that is, a child with a defect in brain development may be otherwise completely normal). Other times, the impairment of brain growth which occurs in craniosynostosis represents one feature in a multiple malformation syndrome. In most children in the former category, the cause of the defect and the risk of recurrence in other siblings are unknown. In some, an autosomal recessive mode of inheritance has been implicated; and in these instances the recurrent risk would be 25 percent. In a multiple malformation syndrome, the cause may be chromosomal, genetic or teratogenic. (The primary teratogenic cause is an intrauterine viral infection.)

Several clinical clues may be used to help distinguish between craniosynostosis due to decreased growth of the brain, and craniosynostosis due to a defect in sutural development:

- Children with secondary craniosynostosis frequently have a head circumference which is disproportionately small for their length and weight.
- The rate of head growth is usually substantially decreased in secondary craniosynostosis.
- Children with secondary craniosynostosis

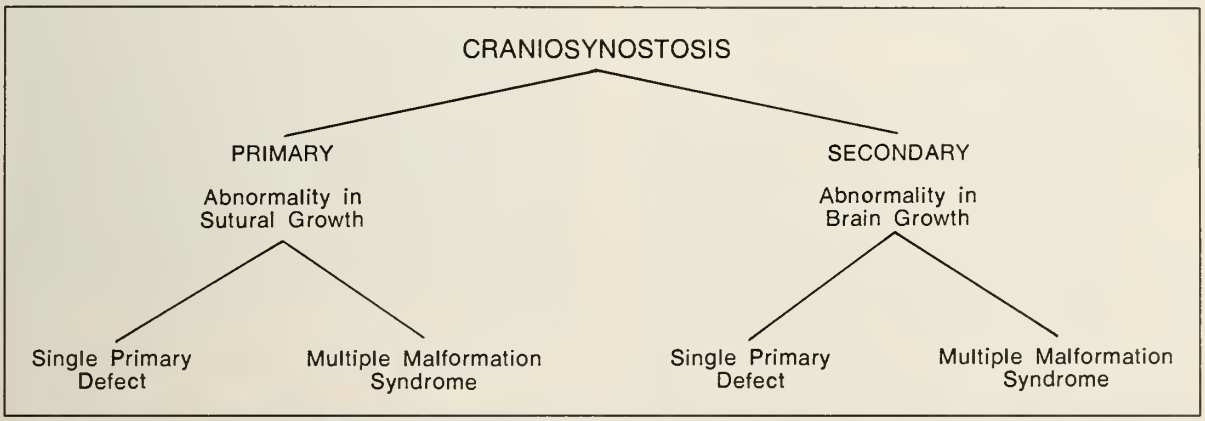

Figure 1.—Schematic classification of craniosynostosis.

TABLE 1.—*Syndromes With Craniosynostosis*

Syndrome	*Cause*
Chromosomal syndromes	
5p+ syndrome[2]	Trisomy for short arm of chromosome 5
7p− syndrome[3]	Deletion of short arm of chromosome 7
13q− syndrome[4]	Deletion of long arm of chromosome 13
Monogenic syndromes	
Apert syndrome[5]	Autosomal dominant
Crouzon syndrome[5]	Autosomal dominant
Pfeiffer syndrome[5]	Autosomal dominant
Saethre-Chotzen syndrome[5]	Autosomal dominant
Carpenter syndrome[5]	Autosomal dominant
Christian syndrome[6]	Autosomal recessive
Summitt syndrome[7]	Autosomal recessive
Baller-Gerold syndrome[5]	Autosomal recessive
Gorlin-Chaudhry-Moss syndrome[8]	Autosomal recessive
Teratogenically induced syndromes	
Aminopterin syndrome[9]	Aminopterin or methotrexate during pregnancy
Sporadic, incompletely delineated syndromes	
Herrmann-Opitz syndrome[10]	?
Herman-Pallister-Opitz syndrome[11]	?
Sakati-Nyhan-Tisdale syndrome[12]	?

have small, normally shaped heads, but because the brain is not growing, none of the sutures remain open. In primary craniosynostosis, on the other hand, the head is frequently asymmetric. The brain is growing at a normal rate but must adjust to the confined space. Thus, it continues to grow in areas where the sutures remain open but not where they have closed. This impairment in growth may lead to an abnormally shaped head.

- In most children with secondary craniosynostosis, neurological findings are abnormal. However, results of neurological examinations early in life usually are normal in children with primary craniosynostosis. In the rare cases of primary craniosynostosis in which all sutures are fused early in life, abnormal neurological findings will probably be noted. As the normal brain continues to grow in these children increased intracranial pressure will develop.

When carrying out a physical examination of a patient with craniosynostosis, it is important to be aware of an additional clinical clue. Structural defects of the limbs are the most common associated anomalies in multiple malformation syndromes associated with primary craniosynostosis. Each of the multiple malformation syndromes listed in Table 1 (except the Crouzon syndrome, the Christian syndrome and the Gorlin-Chaudhry-Moss syndrome) involves a defect in limb development, as well as craniosynostosis.

Reports of Cases

The presentation of a few brief case studies will illustrate the approach that has been outlined. The first case involved a child who was born after a normal 40-week gestation. Delivery was by cesarean section because of breech presentation. The mother noted that the infant had an extremely small head. When first seen by us at three months of age, the infant's head circumference was 34 cm (far below the third percentile). Results of the physical examination were otherwise normal, except for pronounced hypertonicity, irritability and developmental delay. Because of the disproportionately small, normocephalic head and abnormal neurological findings, our impression was that this child had secondary craniosynostosis. Furthermore, because all of the other results of her physical examination were completely normal, we felt that this represented a single primary defect in development. Further evaluation included a careful family history, transillumination of the head, a computerized axial tomographic (CAT) scan, and a study of blood specimens for viral titers. Transillumination showed multiple porencephalic cysts. A surgical

Figure 2.—Left, Frontal view—Newborn infant with asymmetry of the head secondary to synostosis of the sagittal and lambdoidal sutures. **Right,** Side view—Newborn infant with asymmetry of the head secondary to synostosis of the sagittal and lambdoidal sutures.

operation was not felt to be indicated because of the extent of disease in the brain.

The second case involved an infant who was born following a normal pregnancy and delivery. Birth weight and length as well as head circumference were normal. However, the newborn infant had pronounced asymmetry of the head (Figure 2). Results of a physical examination showed no other abnormalities. Based on the asymmetric shape of the infant's head and its normal circumference, and the unremarkable findings on neurological and physical examinations, it was felt that this patient had primary craniosynostosis that involved a single primary defect in an otherwise normal infant. Our evaluation was limited to studying roentgenograms of the skull which showed synostosis of the sagittal and lambdoidal sutures. The infant was referred for a neurosurgical operation.

Figure 3.—Newborn infant with the Apert syndrome. Note the asymmetry of the calvarium, secondary to synostosis of the coronal and lambdoidal sutures.

Figure 4.—The hand of the newborn infant with the Apert syndrome in Figure 3. Note the syndactyly of the fingers.

The third infant (Figure 3) was born after a 37-week, uncomplicated pregnancy and delivery. Birth weight was 2,860 grams (50th percentile), length at birth was 50 cm (75th percentile) and head circumference was 31 cm (10th percentile). There was considerable asymmetry of the craniofacial area. An examination disclosed ridges palpable over the lambdoidal and coronal sutures, hypoplastic supraorbital ridges, orbital hypertelorism, downslanting palpebral fissures and a cleft of the soft palate. In addition, there was bilateral soft-tissue syndactyly of fingers two through five, and of toes two through five as well (Figure 4). Results of the neurological examination showed no abnormalities. Because of the pronounced cranial asymmetry, the normal head circumference, and the unremarkable findings of the neurological examination, this infant was felt to have primary craniosynostosis as one feature of a multiple malformation syndrome. The features of this disorder are those of the Apert syndrome. Evaluation included roentgenograms of the skull, which showed synostosis of the lambdoidal and coronal sutures. A CAT scan was done to rule out a possible hydrocephalus. The infant was referred for a neurosurgical operation. Having made a diagnosis of the Apert syndrome, it was possible to give the family accurate counseling on the risk of recurrence. The Apert syndrome is an autosomal dominant disorder; both parents were normal, indicating that this child represented a fresh gene mutation. The risk of recurrence was 0 percent.

HECTOR E. JAMES, MD:* The most common form of primary synostosis is scaphocephaly, a condition in which the head growth cannot occur in

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the transverse axis because of fusion of the sagittal suture. Instead, growth occurs primarily at the coronal, frontal, parietotemporal and lambdoidal sutures.[13] The next most common sutural involvement in primary synostosis is coronal synostosis; the unilateral form is more common than the bilateral form. In the bilateral form, the characteristic situation is a broad, high forehead. It has been observed that a combination of coronal and lambdoidal synostosis will produce oxycephaly or turricephaly (a tower-shaped head), because the only opening is the sagittal suture and the anterior fontanelle. Thus, it is clear that a thorough examination of a child with a significant calvarial abnormality is essential for diagnosing the syndrome and determining the location of the synostosis. Unfortunately, in children with partial syndromes, problems occur which frequently go unrecognized. In the past, these children would present with other disorders, such as later neurological handicaps, because of the impairment of brain growth.

Treatment of Synostosis

The primary objective of a surgical operation for synostosis is to allow adequate growth of the brain. The secondary objective is cosmetic. I want to emphasize the primary objective. The bulk of the brain's growth occurs by 12 months of age. When one looks at brain length, one sees that by one year of age it has already reached 80 percent of the full growth achieved in adulthood.[13,14] Therefore, if any problem occurs in the development of the calvarium, and it occurs within the first few months of life, as is often the case, the growth of the entrapped brain will be impaired. Under these conditions, signs and symptoms of increased intracranial pressure may develop, such as motor and developmental retardation or optic atrophy. Thus, although the brain can affect the development and molding of the calvarium of the cranial vault because of its tremendous force of expansion, early detection and prompt surgical treatment are extremely important for a positive end result.[14] It was recognized by some of the pioneers in the surgical treatment of this disorder that so-called simple synostosis or single-suture synostosis probably does not exist as an entity.[14]

Plain x-ray films represent a static way of looking at a pattern of sutural growth. We have tried to look at the synostosis more dynamically. A plain skull film may not be relevant because of motion artifact. We have had better results in looking at suture activity with isotope scanning, and this technique has provided us with insights into the disease process that we previously did not have. For instance, we have seen the lack of suture activity in some children because the suture is completely closed; in others the suture is inactive because of other underlying disease processes with which we are not entirely familiar.

We wish to present a classic case of scaphocephaly, to illustrate this approach. The plain x-ray films were not adequate. The diagnosis made was of lambdoidal synostosis, based on the presence of a very prominent ridge over the back of the head. However, there was an excessive anteroposterior length indicating scaphocephaly which could only be a consequence of sagittal closure. An isotope scan of the skull disclosed no coronal activity in this child at all. The posterior view showed an absence of activity in the lambdoidal suture line. The vertex view is the best one for observing the sagittal suture, and we could see a very hazy image, indicating that the suture was not turning over bone adequately. However, the most important feature of this patient's condition was not confirmed until during the surgical operation. Not only were the lambda and the sagittal sutures involved, but the coronal sutures were closed as well. Therefore, this child did not need the linear sagittal or lambdoidal craniectomy, but rather a more extensive surgical reconstructive procedure. We have discovered that this is the more common form of scaphocephaly, rather than the so-called simple or single-suture synostosis.

The first large series of patients were treated with surgical techniques instituted at the Boston Children's Medical Center,[13] and subsequent variants of these methods have been developed. As an example, one of the original techniques for avoiding the area of the sagittal sinus in treating scaphocephaly was the parasagittal craniectomy. After removing the bone on each side of the sagittal sinus, a synthetic material was interposed between the opening in the bone so as not to allow growth between the two edges of bone. In this way, the transverse diameter of the skull was increased. This is the most unsatisfactory procedure from a cosmetic point of view. The patient came to the operating room with a long head and left the operating room with a long head. This type of procedure is also followed by a fairly high incidence of recurrence.[13,14] At present the pre-

ferred treatment for scaphocephaly, recognizing that there is more than just simple sagittal synostosis, is a multiple-suture synostectomy, with a total reconstruction of the calvarium. The incidence of recurrence is nil, and the cosmetic result is very good.[15]

JACK C. FISHER, MD:* Dr. Jones has outlined several syndromes in which deformities of the cranium and those of the face occur. Dr. James has provided an up-to-date summary of the current understanding regarding the origins of, and appropriate therapeutic response to, premature fusion of cranial sutures. Furthermore, he has hinted that the deformity we can see and feel may be a result of primary disturbances within the cranial base. I wish to discuss problems of the basal region further in order to explain the basis for our desire to avert facial deformity at the time of cranial synostectomy.

Nearly every new concept, by the time it achieves widespread acceptance, has for its origin a basic observation recorded well in advance of the time it could be fully understood or applied clinically. For example, we can look back to 1955 when Melvin Moss,[16] an orthodontist, summarized a series of rodent experiments in which a morphologic basis for the common cranial deformities that accompany synostosis could be defined. His cautious analysis of data derived from animal studies has not only survived the test of time, but also has proved applicable to humans. Moss proposed that ordinarily, cranial synostosis was secondary to another primary event. Malformations at the base of the skull preceded union of the cranial sutures. The fetal neural skull was considered to include a base, a neurocranial capsule, and a neural mass or primordial brain. Within the capsule, the dura and calvarial bones differentiated, the capsule retaining its attachment to the cranial base. Finally, according to Moss, the ultimate morphologic destiny of the cranium and facial mass appeared to be a derivative of brain growth on the one hand, and the restraining influence of the capsular attachments to the cranial base on the other. According to this hypothesis, dyscephaly in the form of cranial fusion becomes a manifestation or result of neurocranial malformation, rather than a primary cause. Thus, coronal synostosis can be considered the result of spatially malformed sphenoid wings, whereas sagittal synostosis is the result of a variation in dural attachments to the crista galli and cribriform plate. We have since learned of more subtle variations in cranial base sutures (the ethmofrontal and sphenofrontal sites of bony union) which, until recently, were beyond the site of gross radiologic inquiry, and certainly beyond the range of palpating fingers.

What does this mean to a specialist charged with the responsibility of preventing brain compression, or to a pediatrician who first perceives the presence of early sutural union? The answer is related in part to another frontier, largely technical, which has permitted correction of many of the major craniofacial malformations as well as stimulated a reexamination of their origin. The pioneering work of the French surgeon Paul Tessier[17] prompted a more courageous surgical approach to severe facial deformities. Tessier's original work was done almost exclusively on adolescents and early adults with fully developed deformities (such as craniofacial dysostosis, also called the Crouzon syndrome). His was a largely technological contribution, extending principles learned by plastic surgeons during the world wars while treating extensive maxillofacial injuries, and relying on simultaneous exposure of the anterior brain vault and facial skeleton.[17]

Soon the obvious questions were asked: why not intercept these deformities at an earlier age,[14] and can their full expression be prevented by early surgical intervention—that is, within a few weeks of birth? The answer to both questions was yes. Mohr, Hoffman and associates[14] have recorded the association between cranial and facial malformations presumed to originate from the cranial base. They have also led the movement to correct the origins of the facial components of these deformities well in advance of their full expression. One example is the identification of the periorbital components of unicoronal and bicoronal synostosis, with associated retrusion of the brow(s) and shallowness of the orbit(s). It can be presumed that if left alone, these orbital synostoses will ultimately lead to craniofacial dysmorphism of the Apert or Crouzon variety. Experience with surgical advance of the restrained orbital rims suggests that permanent deformity may be averted, particularly when orbital repositioning can be carried out very soon after birth.

Conclusion

The lessons, some old and some new, can be listed as follows: (1) Primary craniosynostosis

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may never be a primary event, but rather a result of abnormal development at the cranial base. (2) Malformations of the cranium are often associated with malformations of facial development. (3) Clinicians faced with a child with craniosynostosis are also presented with an urgent need to prevent brain entrapment, as well as an opportunity to halt progression of the facial deformity. (4) Finally, proper management of this array of developmental disorders requires close communication between several specialists, including a pediatric dysmorphologist, a neurosurgeon and a plastic surgeon.

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Relationship of Caffeine to Fibrocystic Disease

JOHN P. MINTON at Ohio State University in Columbus has worked for a number of years studying the effects of adenosine monophosphate levels in breast tissue. As an offshoot of that, he became interested in . . . substances called methylxanthenes. Caffeine—such as in coffee, tea, colas and cocoa—belongs to the methylxanthene group. These seem to inactivate a hormone which should stop the action of drugs that stimulate activity within the cell to produce fibrous tissue and cyst fluid. On the presumption that the consumption of methylxanthene in the form of caffeine is a cause of fibrocystic disease, Minton and his group eliminated caffeine from the diet of women with symptomatic lumpy fibrocystic disease. . . . Of 20 patients who were having ongoing and continuing symptomatic troubles, 13 had complete resolution of the process. . . . Of a group of 27 who continued to consume coffee, tea, colas, and so forth, only one had a corresponding regression. The long-term follow-up studies have continued to confirm the results. . . . There is a strong suggestion that caffeine, as one of the methylxanthene group, may well have something to do with the perpetuation of and increase of symptoms of fibrocystic disease.

—ELMER K. SANDERS, MD, *Houston*

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Perspectives on Craniosynostosis

M. MICHAEL COHEN, JR., DMD, PhD, *Seattle*

A SPECIALTY CONFERENCE on craniosynostosis and craniofacial anomalies precedes this article.

The term *craniostenosis* was introduced by the great German pathologist Virchow in 1851.[1] More recently, the word *craniosynostosis* has been used by Ingraham and other Americans.[2] Technically, craniosynostosis is the process of premature sutural fusion, craniostenosis the result.[3] Actually, the terms have been used interchangeably, although in recent years, craniosynostosis seems to be replacing craniostenosis as the more common term.

Anatomic and Genetic Perspectives on Craniosynostosis

Different classifications of the same phenomenon may be equally valid for different purposes. Craniosynostosis can be viewed from two different perspectives—anatomic and genetic. When the main interest is clinical description, growth and development, or surgical management of craniosynostosis, the perspective is anatomic. In this context, which particular suture is synostosed is of primary importance. In genetic perspective, classifying syndromes on the basis of which particular suture is synostosed can be very misleading. Because patients with the *same* genetic condition may have fusion of *different* sutures (Figure 1), which specific suture is synostosed is of secondary importance in this context. The clinical geneticist's main concern is with the overall pattern of anomalies (from which diagnosis of syndromes follows) and with those family members who are affected (from which genetic counseling follows). Thus, in genetic perspective, craniosynostosis and syndromes with craniosynostosis should not be classified on the basis of which sutures are synostosed.[4]

Types of Craniosynostosis

We can define several different types of craniosynostosis, and three pairs of terms will be introduced to accomplish this. First, craniosynostosis may be either simple or compound. In *simple* craniosynostosis, one suture is prematurely fused. An example is coronal, sagittal or lambdoidal synostosis. In *compound* craniosynostosis two or more sutures are synostosed. A patient with early obliteration of both coronal and sagittal sutures has compound craniosynostosis, as does a patient with coronal, sagittal and lambdoidal synostosis.

Second, craniosynostosis may be designated as either primary or secondary. *Primary* craniosynostosis is the most common type of craniosynostosis and examples have already been given above under *simple* and *compound* craniosynostosis. Why, then, is such a designation necessary? This can best be answered by defining secondary craniosynostosis, the polar term of the pair. In *secondary* craniosynostosis, sutural obliteration is secondary to a known disorder. For example, in thalassemia, thickening of the skull may lead to sutural obliteration. Some cases of hyperthyroidism may result in sutural fusion. In microcephaly, failure of brain growth may lead to early fusion of sutures. Thus, secondary craniosynostosis may be observed in various hematologic disorders, metabolic disorders and malformations.

Finally, craniosynostosis may be either isolated or syndromic. In *isolated* craniosynostosis, the patient has no other abnormalities except those that may occur secondarily to early sutural oblit-

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eration, such as neurologic or ophthalmologic manifestations. Patients with coronal synostosis and patients with combined sagittal and lambdoidal synostosis serve as examples. In contrast, *syndromic* craniosynostosis occurs with other primary defects of morphogenesis. In the Carpenter syndrome, for example, polysyndactyly and, frequently, congenital heart defects accompany craniosynostosis.

Classifications of Craniosynostosis and Their Limitations

Classifications of craniosynostosis based on anatomic considerations are numerous and many problems are encountered in their use. However, what is most important is a clear description of which suture or sutures are involved and the extent of involvement, irrespective of classification.

Seven problems inherent in most anatomic classifications of craniosynostosis should be mentioned: (1) Many terms have been used inconsistently. For example, oxycephaly has been used not only to designate premature synostosis of all cranial sutures, but also for synostosis of the coronal plus one other suture. (2) There are no designations for some forms of simple craniosynostosis. The term brachycephaly may be used for coronal synostosis and the term scaphocephaly for sagittal synostosis; however, there are no well-accepted terms for simple synostosis of the lambdoidal or squamosal sutures. (3) Designations used to describe craniosynostosis may also be used to describe skull shape without craniosynostosis; brachycephaly or trigonocephaly are examples. (4) Anatomic classifications do not deal adequately with partial or unilateral synostosis. (5) Designations for some forms of compound craniosynostosis do not exist. For example, there are no terms for craniosynostosis involving the sagittal and lambdoidal sutures or for the binary combination of sagittal and metopic synostosis. (6) Anatomic classifications usually do not take into account various sutures and synchondroses of the cranial base. (7) Finally, craniosynostosis may be a singularly inappropriate term for some conditions. For example, in alobar holoprosencephaly, a metopic suture may not be present. Because a proper suture may not form to begin with, the term craniosynostosis does not seem to reflect what actually happens.[5]

Simple Craniosynostosis

It is readily apparent in all surveys that sagittal involvement represents the most common type of simple synostosis. There is close agreement among them, with percentages ranging from 56 percent to 58 percent. Males are much more commonly affected than females. Coronal synostosis occurs less frequently than sagittal synostosis, estimates varying from 18 percent to 29 percent. With coronal involvement, females are more commonly affected than males. Metopic synostosis, lambdoidal synostosis and various forms of compound synostosis occur less frequently.[4]

Craniosynostosis and Mental Deficiency

Craniosynostosis and syndromes with craniosynostosis should not be classified on the basis of presence or absence of mental deficiency. It cannot be stated categorically that mental retardation occurs in one craniosynostosis condition but not in another. The risk of retardation is probably present to some extent in all conditions that involve craniosynostosis. Some conditions have a higher frequency of retardation and, in some, the degree of mental retardation tends to be more severe. Certainly, the risk of mental deficiency is

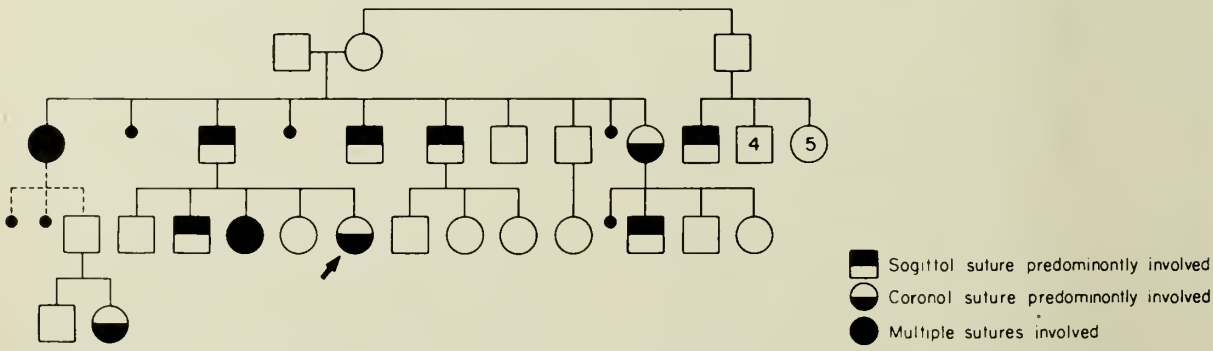

Figure 1.—Autosomal dominant inheritance of simple craniosynostosis, illustrating variability of sutural fusion. Arrow indicates proband. (Modified from Herrmann J, Pallister PD, Opitz JM: Craniosynostosis and craniosynostosis syndromes. Rocky Mt Med J 66:45-56, May 1969.)

TABLE 1.—*Summary of Syndromes With Craniosynostosis**

Types of Syndromes	*No. of Syndromes*
Chromosomal syndromes	11
Monogenic syndromes	26
Autosomal dominant	12
Autosomal recessive	12
X-linked	2
Teratogenic syndromes	2
Total syndromes with known genesis (all categories above)	39
Unknown genesis syndromes	18
TOTAL	57

*From Cohen.[4]

TABLE 2.—*Types of Malformations Most Commonly Associated With Syndromes Having Craniosynostosis**

Types of Malformation	*Percent*
Limb defects	84
Syndactyly/polydactyly	30
Deficiency	22
Other defects	32
Ear anomalies	38
Cardiovascular malformations	23

*From Cohen.[4]

higher with coronal than with sagittal synostosis, higher with bilateral coronal synostosis than with unilateral coronal synostosis and higher with multiple sutural synostosis than with coronal synostosis. Retardation accompanies the Apert syndrome much more frequently than it accompanies the Crouzon syndrome; nevertheless, some patients with the Crouzon syndrome may be retarded. Although in most reported cases, patients with the Pfeiffer syndrome have normal intelligence, some are retarded. It was once thought that the Carpenter syndrome was always associated with severe mental deficiency. However, cases of patients with normal intelligence have come to light.[4,6]

Associated Anomalies and Syndromes

Of syndromic craniosynostoses, many represent known syndromes which have heterogeneous causes, most commonly genetic. However, many other instances of craniosynostosis are associated with a variety of different anomalies, and this group needs to be further delineated. In general, associated anomalies are much more common with coronal synostosis than with sagittal synostosis. A higher than expected incidence of congenital heart defects is observed with both bilateral coronal synostosis (5 percent) and sagittal synostosis (4 percent).[7,8]

Classifying various syndromic craniosynostoses, either as a group or together with isolated craniosynostosis, is fraught with danger. Because causes are known to be heterogeneous, the pathogenesis of craniosynostosis may be heterogeneous as well. Thus, clinical features, growth and development, natural history and results of surgical operations in different conditions associated with craniosynostosis should be separated in analysis, both from each other and from various isolated forms of craniosynostosis.

In recent years, many newly recognized syndromes with craniosynostosis as a feature have come to light. Many more such syndromes will be delineated in the future. Table 1 summarizes the various types of syndromes with craniosynostosis known at present. Of syndromes with known genesis, most are monogenic. It is interesting to note that there are as many autosomal recessive syndromes as there are autosomal dominant ones. Just a few years ago, it was thought that craniosynostosis was not associated with chromosomal syndromes. Today, it is apparent that at least 11 chromosomal syndromes have craniosynostosis as a variable feature. Of the 57 known syndromes with craniosynostosis, the most common are the Crouzon syndrome, the Apert syndrome and the Saethre-Chotzen syndrome. All 57 syndromes have been reviewed recently.[4]

Analysis of syndromes in which craniosynostosis is a feature shows that certain types of anomalies occur more commonly than others. These are listed in Table 2. Evaluation of the limbs, ears and cardiovascular system gives the most significant data for diagnosing syndromes with craniosynostosis. Obviously, abnormalities of the eye and brain occur with high frequency and are important. They are not included here simply because so frequently they are secondary to craniosynostosis. Our concern is with the overall pattern of primary anomalies, from which diagnoses of various syndromes can be made.

Diagnostic Considerations

When craniosynostosis is suspected, the workup should include examination for lack of movement of the calvarial bones in infancy or for palpable ridging (especially with sagittal synostosis), in addition to multiple skull radiographs. If the findings on radiographs are abnormal or cannot be interpreted with certainty, skull scintigraphy may aid in assessing the problem.[9] If a definitive decision cannot be made, a cephalic index (maxi-

mum head breadth/maximum head length × 100) should be taken. A change in the cephalic index over time is significant. The patient should also be evaluated for the presence or absence of various anomalies, keeping in mind that the most significant data for syndrome diagnosis come from evaluating limb defects, ear anomalies and cardiovascular malformations (Table 2). When appropriate, family history should be supplemented by snapshots, a physical examination, or both.

An attempt should be made to distinguish between primary and secondary craniosynostosis (Figure 2). In primary synostosis, the head shape is more likely to be abnormal and may be associated with asymmetry. In contrast, when craniosynostosis results secondarily from microcephaly, the head is often normally shaped, but disproportionately small. A clinical corollary to this distinction is that surgical intervention in primary craniosynostosis may be very effective, assuming that there is no underlying central nervous system malformation. On the other hand, surgical intervention is not effective for most cases of secondary craniosynostosis.

Most instances of isolated, primary craniosynostosis are sporadic. The risk of recurrence in such situations is assumed to be extremely low. If parent and child are affected, the risk for subsequent affected children approaches 50 percent. If two siblings are affected and both parents are normal, the risk for subsequent affected children approaches 25 percent. With instances of monogenic, isolated craniosynostosis, dominant inheritance occurs much more frequently than recessive inheritance. An exception occurs with familial, simple craniosynostosis involving the sagittal suture, in which a multifactorial recurrence risk can be given.[4,7,8]

When primary craniosynostosis is found in association with other anomalies, the clinician should strive to diagnose the overall condition to provide a rational treatment plan and proper counseling on the risk of recurrence. The 57 known syndromes with craniosynostosis have been discussed elsewhere.[4] At present, syndromes with craniosynostosis and syndactyly, polydactyly or polysyndactyly are very likely to be monogenic (Figure 2). In contrast, if the limb defects are of the *deficiency* or *other defect* type, and occur with growth deficiency of prenatal onset, the condition is more likely to be chromosomal or even terato-

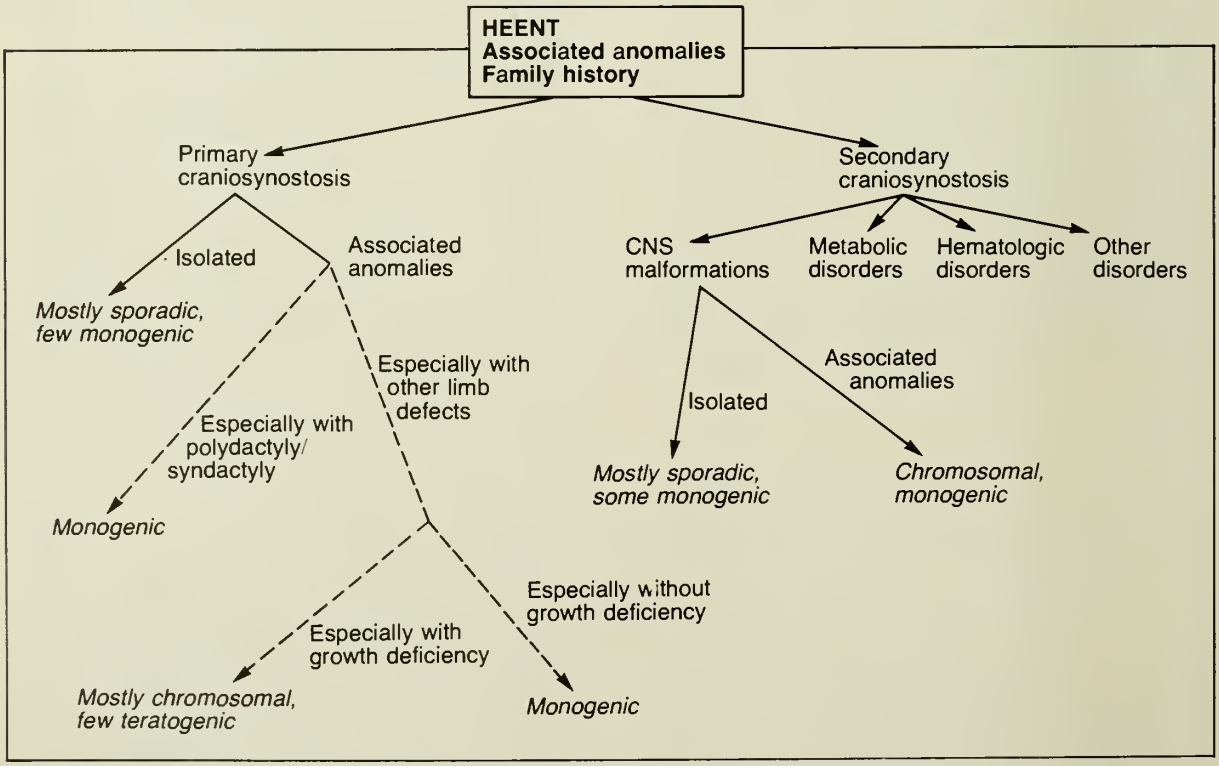

Figure 2.—Flow chart indicating diagnostic considerations in craniosynostosis. Dashed lines indicate that there are a few exceptions to flow sorting. (HEENT = head, eyes, ears, nose and throat)

genic. In the absence of growth deficiency, the condition is likely to be monogenic.

Secondary craniosynostosis (Figure 2) may be observed with central nervous system malformations (such as microcephaly and encephalocele), metabolic disorders (such as hyperthyroidism, rickets and the Hurler syndrome), hematologic disorders (such as various thalassemias and sickle cell anemia) and other disorders (for example, ataxia-telangiectasia, epidermal nevus syndrome and the Job syndrome).[4] Certainly, synostosis tends to be a variable and only occasionally observed abnormality in such disorders. Furthermore, many other signs and symptoms are present which serve as diagnostic clues to these conditions.

The Association of Facial Malformations With Craniosynostosis

Facial malformations are known to accompany some instances of craniosynostosis. Well-known examples include the Apert syndrome and the Crouzon syndrome. However, craniosynostosis per se is not invariably associated with facial anomalies, nor are such malformations always secondary to premature sutural fusion. Craniosynostosis may occur with facial malformation when coronal synostosis is accompanied by sphenofrontal and frontoethmoidal sutural synostosis. Facial anomalies may also occur with true hypoplasia of the cranial base or of the nasomaxillary complex, or with fusion of facial sutures. It is important to point this out because some oversimplified schemes describe synostosis of the coronal suture as automatically producing an arrest of facial growth, resulting in facial malformation. This view seems to have arisen from observing the unilateral upper facial flattening that accompanies unilateral coronal synostosis in infancy. However, the skull is composed of numerous bones whose many articulations allow some degree of compensatory adaptation. This may allow normalization depending on the severity of the lesion and the time that it was initiated during growth. A quotation from the excellent study of methyl cyanoacrylate-induced synostosis of the coronal suture in rabbits[10] serves to make the point.

> Results from our study documented the independence of calvarial and facial growth. Although there were immediate changes in facial orientation following immobilization of the coronal suture, these changes were ameliorated with further development. This may indicate that the compensatory facial adjustment to the calvarial deformity was insufficient in the initial stages when the neurocranial growth rate far exceeded the facial growth rate.

Bertelsen[11] and others have documented many cases of coronal synostosis in humans in which no facial abnormalities accompany the condition. Finally, it should be noted that facial malformations may occur *without* craniosynostosis in conditions usually associated with premature sutural fusion. In the Crouzon syndrome, cases have been observed in which ocular proptosis and midface deficiency have occurred in the absence of craniosynostosis; however, classic examples of the Crouzon syndrome with craniosynostosis have been observed in the same family as well. Midface deficiency and classic syndactyly have been observed in patients with the Apert syndrome in the absence of craniosynostosis.[4]

Craniofacial Surgical Procedures

Recent developments in craniofacial operations are exciting. In the forefront of the explosion of new surgical techniques are Tessier,[12-14] Converse,[15,16] Edgerton,[17] Jane,[18] Mohr,[19] Murray,[20,21] Sayers[22] and others.[23-25] The new procedures offer great hope for affected persons. Although the results have been dramatic, most of them are reported in anecdotal fashion with a few accompanying pictures. Long-term studies to evaluate the results should be the next order of business. At present, different surgeons are using different surgical procedures and the timing for various procedures may differ depending on a variety of different circumstances. Careful documentation of the results over time is essential.

Etiology and Pathogenesis

Three classic theories have been advanced to explain craniosynostosis. Virchow[1] believed that craniosynostosis was a primary malformation and that the associated cranial base deformity was secondary to craniosynostosis. The converse was postulated by Moss;[26] the cranial base malformation was the primary anomaly, resulting in secondary premature fusion of the cranial sutures. In speculating on the pathogenesis of the Apert syndrome, Park and Powers[27] postulated a primary defect in the mesenchymal blastema that led to both craniosynostosis and an abnormal cranial base.

Currently, Moss's theory is the most popular of the three. Unfortunately, most discussions of craniosynostosis assume that there is a single patho-

genetic mechanism that remains to be elucidated, and that once this is done, alternative hypotheses will be shown to be incorrect. Syndrome delineation and clinical evidence to date strongly suggest that craniosynostosis is pathogenetically heterogeneous. Some 57 different syndromes have been recognized in which craniosynostosis is a feature (Table 1). Some are known to be and others are presumed to be etiologically heterogeneous. Such etiologic heterogeneity, of course, suggests the possibility of pathogenetic heterogeneity. Thus, all three theories are probably correct; each may be implicated in some, but not all, cases of craniosynostosis.

According to Moss's theory, spatially malformed lesser sphenoidal wings in coronal synostosis, and spatially malformed cribriform plate and crista galli in sagittal synostosis are viewed as primary abnormalities which, at the points of dural attachment, transmit aberrant tensile forces upward through the dura, leading to premature fusion of the overlying sutural tissues.

Many familial instances of isolated (nonsyndromic) craniosynostosis have been observed.[4] Most instances are compatible with autosomal dominant transmission. In some families, involvement is variable—some family members having fusion of the sagittal suture, some having fusion of the coronal suture and still others having synostosis of both coronal and sagittal sutures (Figure 1). It is difficult to conceive of dramatically different primary abnormalities of the cranial base occurring in the same family as a dominant trait. Thus, a different pathogenetic mechanism than the one proposed by Moss[26] may be operative in such families.

A primary abnormality of the cranial base as the cause of craniosynostosis in the Apert syndrome has been proposed by Moss[26] and supported by Stewart.[28] However, clinical evidence to date indicates that the pathogenetic mechanism for craniosynostosis in this syndrome may possibly be unique. Features of the Apert syndrome include progressive calcification and fusion, with time, of the bones of the hands, feet and cervical spine.[29] Progressive generalized bony dysplasia with ankylosis of joints as well as progressive limitation of motion at these joints have been documented.[30] Finally, progressive calcification of the cartilaginous nasal septum and stylohyoid ligament has also been observed.[30] The most frugal hypothesis would be that whatever mechanism is responsible for progressive calcification throughout the body is also responsible for premature craniosynostosis in the Apert syndrome. Because neither the cranial base nor the points of dural attachment can be invoked to explain progressive calcification elsewhere, it is probable that they have nothing to do with craniosynostosis in the Apert syndrome either.

Recently, Persson and his co-workers[10] showed that craniosynostosis occurred after the experimental application of methyl cyanoacrylate adhesive to the coronal suture in 9-day-old rabbits. The resultant immobilization produced constraint of growth stretch across the sutural area which, presumably, caused craniosynostosis to occur. Graham and colleagues[31] hypothesized that, in similar fashion, human prenatal head constraint may be responsible for some cases of craniosynostosis. They noted that some mothers of infants with isolated sagittal synostosis gave a history of early descent of their abdominal silhouette and severe pelvic pressure during the last one to three months of gestation. These symptoms were interpreted as a sign of early descent of the fetal head into the lower pelvis.

Lack of growth stretch at the sutures may also be implicated in three malformations in which premature craniosynostosis may occur as a complicating feature. First, sutural fusion may accompany some cases of microcephaly.[32] Lack of central nervous system growth may result in lack of growth stretch across the sutural areas, producing secondary craniosynostosis. Second, several reports have linked shunted hydrocephaly to craniosynostosis.[33,34] Low pressure systems may be implicated, in which growth stretch at the sutural areas suddenly becomes totally deficient. Finally, some cases of encephalocele have been associated with craniosynostosis.[35] Such "blow-out" lesions may sometimes result in lack of growth stretch across the sutures.

Premature craniosynostosis may result from several dysmetabolic states. It has been observed to accompany hyperthyroidism during childhood.[36-38] Sutural fusion may be caused by primary thyroid hyperplasia, but more commonly results from excessive thyroxine treatment for congenital hypothyroidism.

Premature sutural fusion may also occur in the Hurler syndrome, which is characterized by α-L-iduronidase deficiency. Craniosynostosis involves the sagittal and lambdoidal sutures.[39]

Craniosynostosis has been observed in various etiologically distinct forms of rickets, in-

cluding vitamin D-deficiency rickets, simple hypophosphatemic rickets, hypophosphatemic-hypocalcemic-aminoaciduric rickets, hypophosphatemic-aminoaciduric-cirrhotic rickets, azotemic osteodystrophy and hypophosphatasia. The extent of synostosis is related to the severity of the rachitic process. Premature sutural fusion was observed in a third of 59 rachitic children under 9 years of age in the study of Reilly and associates.[40]

Craniosynostosis may occur in various hematologic disorders. Hyperplasia of the marrow with compensatory bony overgrowth of the calvaria can "lock" the sutures. Conditions known to result in premature fusion of sutures include the thalassemias, sickle cell anemia, congenital hemolytic icterus and polycythemia vera.[32,41]

Premature fusion of sutures may occasionally accompany a variety of miscellaneous disorders as an abnormality. These conditions include, among others, ataxia-telangiectasia,[42] the epidermal nevus syndrome[43] and Job syndrome.[44] The pathogenesis in such instances is completely obscure.

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Hepatoma

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *In this Medical Grand Rounds an outstanding program in gastroenterology is presented. Among the topics is hepatoma. The chief medical resident, Dr. Richard Locksley, will present a case summary.*

DR. LOCKSLEY:† The patient was a 36-year-old black woman who was admitted for evaluation of hepatomegaly. In 1971 minimally elevated findings of liver function tests were first noted, although the patient was asymptomatic. In 1972 positive results of an antinuclear antibody test were noted. Between 1973 and 1976 slightly elevated levels of serum glutamic oxaloacetic transaminase (SGOT) of between 89 and 110 IU per liter were observed. Determinations for hepatitis B surface antigen (HBsAg) were negative. In December 1976 a liver biopsy was done at another hospital; it showed early macronodular cirrhosis and evidence of chronic active hepatitis. Between 1977 and 1979 the patient had fluctuating episodes of right upper quadrant pain, fatigue and malaise; these complaints increased over the few months before admission, and finally culminated in her first admission here at the University of California, Moffitt Hospital in March 1979. Her past history was remarkable for mild hypertension, which was controlled with hydrochlorothiazide, and for rare alcohol use. She was married and employed.

On physical examination the patient appeared healthy and alert. Her blood pressure was 140/88 mm of mercury. She was anicteric, and there was no lymphadenopathy. The liver span was 18 cm to percussion, and was palpable 9 cm below the right costal margin. It was slightly nodular and minimally tender. There was no bruit, ascites or spleen tip appreciated on that admission. She had no edema or clubbing, and there was no asterixis.

Laboratory data were remarkable for a hematocrit of 37.7 percent, leukocyte and differential counts within normal ranges, a platelet count of 182,000 per cu mm and an erythrocyte sedimentation rate of 65 mm per hour. SGOT was twice normal at 113 IU per liter, lactic dehydrogenase was 111 IU per liter and alkaline phosphatase was 76 IU per liter, which was normal. Bilirubin was 1.1 mg per dl and albumin 3.8 grams per dl with a total protein of 8.8 grams per dl. Prothrombin time was normal at 11.8 seconds and cholesterol was 284 mg per dl. Antinuclear antibody (ANA) was positive at 1:320 in a diffuse pattern. Hepatitis B surface antigen and core antibody determinations were negative. Serum protein electrophoresis showed an alpha-fetoprotein spike with a level

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†Richard Locksley, MD, Chief Medical Resident.

ABBREVIATIONS USED IN TEXT

HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HCC = hepatocellular carcinoma

TABLE 1.—*Conditions Predisposing to Hepatoma*

Cirrhosis due to:
Hepatitis B virus (HBV)
Hemochromatosis
Alpha-1-antitrypsin deficiency
Alcohol
? Chronic active hepatitis
Pharmacological and chemical agents:
Aflatoxin
Androgenic steroids
Thorotrast
? Estrogenic steroids
? HBV infection

greater than 5,000 ng per ml. Results of a right upper quadrant ultrasound test showed a normal gallbladder and biliary tree, but raised the question of thrombus in the portal vein. Findings at laparoscopy disclosed a shrunken liver with evident macronodular cirrhosis and a small amount of ascites. Cytologic and culture findings indicated that the ascitic fluid was benign. However, results of a repeat biopsy showed chronic active hepatitis and macronodular cirrhosis. Just before discharge, a computerized tomographic scan was done, which disclosed a large right hepatic lobe mass that was invading the portal vein and the inferior vena cava. The posterior position of this mass precluded its being seen at laparoscopy. She was readmitted a week later for a percutaneous liver biopsy, which showed poorly differentiated hepatocellular carcinoma. A month later she returned with progressive symptoms, and hepatic radiotherapy and chemotherapy were begun. Her course was one of rapidly progressive disease. She was admitted in August 1979 and had a LeVeen shunt placed for intractable ascites; she was readmitted later that month with a variceal hemorrhage. She was encephalopathic, grossly icteric and edematous at that time. Her bleeding was controlled with vasopressin (Pitressin), vitamin K, lactulose, fresh frozen plasma and blood products, whereby her condition was apparently stabilized. She was discharged home, but returned two hours later with gastrointestinal bleeding and mucosal oozing, and laboratory evidence for disseminated intravascular coagulation. She died soon after admission despite ligation of the LeVeen shunt and other supportive measures.

DR. SMITH: *Thank you, Dr. Locksley. We have asked Dr. David Altman to discuss this case and the general topic of hepatoma.*

DR. ALTMAN:* Hepatocellular carcinoma (HCC) may be the most common type of neoplasm in humans because of its very high incidence in certain areas of the world. Unfortunately, there is an increasing incidence of this form of cancer in the United States. In a review of autopsy material from Los Angeles County Hospital over the past 70 years, Peters and colleagues[1] found that between 1918 and 1953 HCC appeared in approximately 0.15 percent of all autopsies, whereas from 1964 to 1973 HCC was found in nearly 1 percent of all autopsies at that hospital. Also, there seems to be an increased incidence of HCC in noncirrhotic livers.

Cirrhosis of the liver is the disease most commonly associated with the development of HCC (Table 1). Although in the United States alcoholic cirrhosis is the type most often seen in patients with HCC, in other areas of the world, the association is greatest with cirrhosis secondary to hepatitis B virus (HBV) infection. However, in about 25 percent of all cases of HBV-associated hepatocellular carcinoma, no fibrosis in the normal liver is noted. The development of hepatoma in hemochromatosis seems to be a frequent complication and terminal event in this uncommon condition, and usually cannot be prevented by treating the iron overload with phlebotomy. Alpha-1-antitrypsin deficiency is seen with increased frequency in patients with HCC, and alpha-1-antitrypsin-like material has been seen in healthy tissue near the tumor in some patients. However, specific staining using immunohistologic techniques has shown that this material is not alpha-1-antitrypsin, but some other para-aminosalicylic acid-staining material of unknown significance.[2]

Undoubtedly, chronic active hepatitis, particularly chronic active hepatitis due to HBV, is associated with hepatocellular carcinoma. Several pharmacological and chemical agents also are associated with HCC; for example, androgenic steroids have been associated with HCC, particularly in adolescents. One interesting case report described a 14-year-old in whom HCC developed during treatment with androgens for Fanconi anemia. When the administration of androgens

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was stopped, the hepatocellular carcinoma apparently disappeared.[3] Thorotrast, a contrast agent used commonly between 1917 and 1930 in this country, and until the 1950's in Europe, was clearly associated with several different types of hepatic malignancy, including HCC. Because there seems to be a latent period of approximately 20 years between the use of the agent and the development of a malignant condition, there may be a few cases of this still developing now. The association of HCC with estrogenic steroids, particularly those in oral contraceptives, is less strong. However, there have been several somewhat convincing case reports of carcinoma developing in otherwise normal livers of patients receiving estrogenic steroid therapy. The development of HCC in this population, however, is probably even more uncommon than is the development of the rare condition of benign hepatic adenoma.

HBV and Hepatocellular Carcinoma

The association of HBV with hepatocellular carcinoma was among the first important discoveries to follow the detection of the hepatitis B antigen systems in the 1960's. The degree of the association relates directly to the sensitivity of the assay used (Table 2). One or another of the HBV serologic markers was present in 92 percent of the people in Mozambique in whom HCC developed, as opposed to 34 percent in a control population in that country.[4] In the United States, 41 percent of patients with HCC had hepatitis B markers in serum, as opposed to between 1 percent and 8 percent of a control population. Rarely is the hepatitis B "e" antigen seen in patients with hepatocellular carcinoma, and the low incidence of this marker may reflect the indolent nature of the infection required for the development of HCC. In the African and Asian populations the maternal vertical transmission of HBV infection appears important. Larouze and associates[5] studied hepatitis B markers in African patients with HCC, and found that in mothers of the patients tests were more frequently positive for HBsAg than in controls. Interestingly, in the fathers of these patients, tests were positive less often for antibodies to the hepatitis B surface antigen. This difference may reflect an earlier acquisition of the infection and some impairment of immunity.

There seems to be a latent period between the infection and the development of HCC. In Africans HCC develops most often in the fourth decade of life, whereas HBV infection is most likely to occur in the perinatal period. In patients with chronic liver disease, in whom HBsAg or other markers of hepatitis B virus infection are present, HCC develops earlier than in patients who have chronic liver disease but who do not have HBV. Other viruses—including those related to so-called non-A, non-B hepatitis—may be associated with HCC, but less commonly than is the hepatitis B virus.

There are an estimated 176,000,000 carriers of hepatitis B in the world population, with the greatest prevalence in those areas with the highest

TABLE 2.—*Hepatitis B Antigen and Hepatocellular Carcinoma in 16 Studies**

	Hepatoma Patients				*Comparison Groups*		
Country	*Method*	*Number*	*HBsAg*	*Percent*	*Number*	*HBsAg*	*Percent*
USA	MO	12	0	0	2,412	2	0.1
USA	IEOP	55	2	3.6	55,956	58	0.1
USA	IEOP	51	3	5.8	..	..	..
East Africa	MO	11	0	0	511	8	1.5
Uganda	CF	45	18	40.0	122	4	3.3
Senegal	IEOP	210	88	42.0	1,160	140	9.0
Greece	MO	13	4	30.8	..	..	..
Great Britain	RIA	38	9	24.0	..	..	..
Spain	MO	26	9	34.0	900	3	0.3
India	IEOP	11	7	63.6	..	..	0.3
Singapore	IAHA	156	55	35.3	1,516	114	7.5
Hong Kong	MO	42	2	4.7	50	2	4.7
South Vietnam	IEOP	26	0	0	..	..	..
Taiwan	MO	55	44	80.0	943	138	14.6
Japan	IAHA	260	93	37.3	4,387	113	2.9
Japan	IEOP	216	34	15.7	..	..	..

CF = complement fixation; HBsAg = hepatitis B surface antigen; IAHA = immune adherence hemagglutination; IEOP = immunoelectroosmophoresis; MO = micro-Ouchterlony; RIA = radioimmunoassay.

*From Okuda.[13,p77]

incidence of HCC. Szmuness[6] has calculated that the relative risk for the development of HCC in carriers of HBV is 22.6 times greater than that in the uninfected population. Prince[7] has hypothesized that the hepatitis B carrier state itself is the major risk, and that the incidence of HCC is of the same order of magnitude in carriers whether they are in Africa or in the United States.

In Los Angeles Omata and co-workers[8] looked at serum and tissue markers for HBV in patients with both nonalcoholic liver disease and HCC. They then compared the incidence of these markers with their incidence in several other groups, including patients with alcoholic cirrhosis and HCC and persons in a control population. In examining both serum and tissue markers the researchers found an incidence of HBV of up to 75 percent in nonalcoholics with hepatocellular carcinoma (Table 3). Thus, HBV-associated HCC appears to be a problem not only in Africa and Southeast Asia, but in the United States as well.

In 1978, in the United States, the incidence of all types of hepatitis was approximately 30 cases per 100,000, and the incidence of type B hepatitis was approximately 8 cases per 100,000. The incidence in San Francisco was approximately ten times that of the United States as a whole, and in 1977 some 73 percent of cases of HBV occurred in men between the ages of 20 and 39. (S. Dritz, MD, Public Health Department, San Francisco, personal communication, 1980). This subpopulation is likely to have a long life expectancy, and if one approximates a 10 percent incidence of chronic HBV in patients after acute hepatitis B infection, one can foresee a potential risk over the years of a greater incidence of hepatocellular carcinoma in such a local population.

To prove that the hepatitis B virus is carcinogenic, one must show that (1) the infection precedes the development of cancer, (2) the tumor cells contain some apparent or cryptic virus-specific molecules or antigens, (3) the cancer cells produce the virus or virus-specific antigens and (4) the virus can transform cells in culture or induce tumor in experimental animals. Although some evidence exists, such evidence is inconclusive. Certainly it is apparent that hepatitis B infection occurs earlier than the development of hepatocellular carcinoma, particularly in African populations. Tumor cell cultures have been developed which produce hepatitis B surface antigen. Viral deoxyribonucleic acid (DNA) sequences of the hepatitis B virus have been shown to be attached to the host cell DNA, and viral DNA base sequences have been detected in the ribonucleic acid (RNA) of livers infected with hepatitis B virus. Thus, the viral DNA becomes a functioning part of the host DNA.[9]

Other Possible Factors in HCC

Other factors may be involved as well in the development of hepatocellular carcinoma. There is some evidence that HBV alone may not be sufficient to cause HCC in many populations. First, although the risk of HCC in carriers has increased, development of these tumors occurs in very few carriers. In some countries with a high incidence of HBV infection, there is a low incidence of hepatocellular carcinoma. Finally, marmosets given hepatitis B virus plus aflatoxin have a higher incidence of hepatocellular carcinoma than those infected only with HBV.

Aflatoxin

An indicator of other causes of hepatocellular carcinoma is suggested by the observation that the incidence of HCC parallels the intake of certain toxins, especially the mycotoxin aflatoxin. Aflatoxin is produced by *Aspergillus flavus,* a mold that can grow in any warm moist area where grain

TABLE 3.—*Frequency of Positive Test Results for HBV Serum and Tissue Markers in 50 Patients With Hepatocellular Carcinoma and in 63 Control Patients*

	Serum		*Tissue*		*Presence of at least One Tissue or Serum HBV Marker (percent)*
	HBsAg (percent)	*Anti-HBc (percent)*	*HBsAg (percent)*	*HBcAg (percent)*	
Nonalcoholic liver disease and HCC (20 cases)	12 (60.0)	13 (65.0)	11 (55.0)	10 (50.0)	15 (75.0)
Alcoholic cirrhosis and HCC (22 cases)	0 (0.0)	2 (9.1)	1 (4.5)	1 (4.5)	2* (9.1)
Normal liver and HCC (8 cases)	1 (12.5)	1 (12.5)	0 (0.0)	0 (0.0)	1† (12.5)
Alcoholic cirrhosis, control group (63 cases)	3 (4.8)	3 (4.8)	0 (0.0)	1 (0.0)	5* (7.9)

Anti-HBc = antibodies to HBcAg; HBcAg = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma.

*†Significance versus nonalcoholic liver disease and HSS: *$P<0.001$, †$P<0.01$.

is stored. The occurrence of such mold is common in some areas of Africa, particularly in low-altitude terrain, where dietary intake of aflatoxin is substantial (Table 4).[10] In these areas the incidence of HCC seems to parallel intake of aflatoxin. However, in these areas one also sees a high prevalence of HBV infection, making it difficult to determine the relative roles of HBV and aflatoxin. Nevertheless, aflatoxin is a potent carcinogen in experimental animals, including subhuman primates, and is found in products grown outside of Africa and Asia as well. Peanuts are a very common source of aflatoxin and the United States Food and Drug Administration limits the allowable amount in peanut butter to 20 parts per billion. In 1978 *Consumer Reports*[11] reviewed various brands of peanut butter, and found aflatoxin in quantities greater than 20 parts per billion in three of 76 brands tested; it was not detected in only nine of the 76 brands. The conclusion of the consumer publication was that the relatively low levels of aflatoxin detected were not worrisome enough to warrant prohibition of peanut butter which is otherwise relatively nutritious.

Proposed Mechanisms of Hepatocarcinogenesis

The proposed mechanism of chemical hepatocarcinogenesis is reminiscent of that suggested for the hepatotoxicity of certain drugs. A procarcinogen is metabolized by the mixed-function oxidases of the hepatocyte to a proximate carcinogen, acquiring an active radical which binds to the informational content of the liver cell nucleus. When the active compound is bound to the cell membrane and other macromolecules, acute cell injury occurs as opposed to malignant transformation.[12]

With evidence that HBV may not be sufficient for the development of carcinoma, and that aflatoxin also may not act alone, two theories of cocarcinogenesis have evolved. The first is that the virus is itself the carcinogen, and that the chemical cocarcinogen—perhaps aflatoxin—facilitates the incorporation of the viral DNA into the host cell genome, leading to malignant transformation of the hepatocyte; the second theory is that the virus modifies microsomal biotransformation by its effects on DNA and RNA, and thus leads to the increased production of carcinogenetic metabolites of the chemical. A hepatitis virus similar to the hepatitis B virus, but slightly different in its morphological characteristics, infects woodchucks in eastern Pennsylvania. It appears to lead to the same pathological changes in the woodchuck liver, as does the hepatitis B virus in the human liver. Perhaps studies of this animal model will yield more information about hepatocarcinogenesis.

Clinical Features

Hepatocellular carcinoma has highly variable clinical features. The most common are abdominal pain, an abdominal mass and loss of weight. The most common physical finding is hepatomegaly, which is present in approximately 70 percent of patients with HCC; abdominal tenderness is present in about 50 percent.[13] In 90 percent of patients with hepatocellular carcinoma, elevation of alpha-fetoprotein is noted, particularly when measured by a radioimmunoassay. However, it also is elevated in patients with gastric carcinoma that has metastasized to the liver, germ cell tumors, acute hepatitis or chronic active hepatitis. Although serial measurements of alpha-fetoprotein in selected populations of patients known to have cirrhosis have led to earlier detection of carcinoma, rarely are such tumors smaller than 5 cm in diameter when so discovered. Therefore, at this time, alpha-fetopro-

TABLE 4.—*Daily Aflatoxin Intake and Liver Cancer Incidence in Kenya**
(Study Population, Boys and Men 16 Years and Older)

	Altitude Subarea		
	High	*Middle*	*Low*
Frequency of diet contamination	39/808	54/808	78/816
Mean aflatoxin level (ppb)	0.121	0.205	0.351
Frequency of beer contamination	3/101	4/101	9/102
Mean aflatoxin level (ppb)	0.050	0.069	0.167
Mean aflatoxin ingested† ng/kg of body weight/day	4.88	7.84	14.81
Liver cancer incidence	3.11	10.80	12.12

ppb = parts per billion

*From Peers and Linsel.[10]
†Assuming intake of 2 kg of food and 2 liters of beer per day per 70 kg of body weight.

tein measurement has little impact on diagnosis or outcome of HCC.

Newer radiologic tools, including abdominal ultrasound tests and computerized tomography, have been applied to the diagnosis of HCC. Interestingly, in some cases, one or another of these techniques has failed to visualize a large tumor mass in the liver, probably because of the similar radiologic density of the abnormal and normal tissue (Figure 1). Hepatic arteriography remains definitive for diagnosis of hepatocellular carcinoma, but this, of course, cannot be used as a screening technique.

There are many interesting extrahepatic manifestations of HCC (Table 5).[14] The first to be described was hypoglycemia, the most common extrahepatic feature of this disease. Up to 30 percent of patients with hepatocellular carcinoma may become hypoglycemic. The mechanisms involved in hypoglycemia associated with HCC are poorly understood. The hypoglycemia does not seem to relate to increased production of insulin or insulin-like hormones or inhibition of counterregulatory hormones, but may be due to changes in hepatic metabolism of glycogen. Decreased activity of glucose-6-phosphatase has been noted, not only in tumor tissue but also in normal liver tissue, leading to decreased glycogenolysis, in essence an acquired type-1 glycogen storage disease. Erythrocytosis may be related to increased erythropoietin production. Hypercalcemia probably is caused by extraparathyroid parathormone production. Porphyria cutanea tarda is rarely associated with HCC, and the incidence of this may be overestimated because there is a large coincidence of porphyria cutanea tarda, alcoholic cirrhosis and hepatocellular carcinoma.

Although hepatocellular carcinoma may metastasize to many different organs, it primarily invades the lung and lymph nodes. At the time of diagnosis, only 33 percent of patients without cirrhosis and only 50 percent of those with cir-

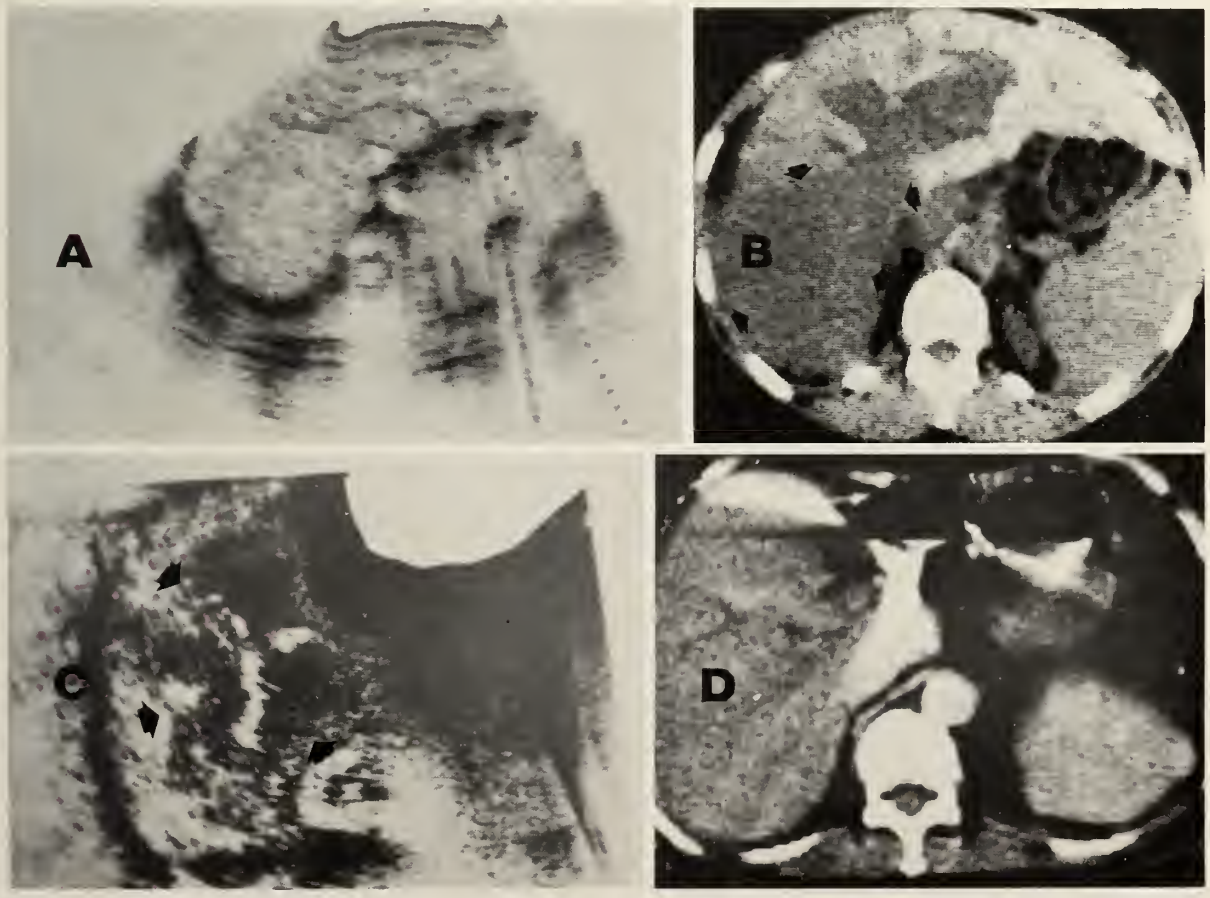

Figure 1.—Neither an ultrasound test nor a computerized tomographic (CT) examination of the liver is completely sensitive with respect to HCC. **A,** Ultrasound test findings of liver in patient with abdominal pain and hepatomegaly. **B,** CT of same patient showing large hepatic mass **(arrows). C,** Ultrasound test results of liver in another patient with a liver mass **(arrows). D,** CT of same area seen in a second patient with no evident hepatic mass.

TABLE 5.—*Systemic Manifestations of Hepatocellular Carcinoma*

Erythrocytosis
Hypercalcemia
Gonadotropin production
Feminization
Hypoglycemia
Hyperlipidemia
Porphyria cutanea tarda
Dysfibrinogenemia
Cryofibrinogenemia
Osteoporosis
Increased vitamin B_{12} binding proteins

rhosis have been found to have no evidence of metastasis.

Treatment

The major approaches to treatment of HCC, including surgical operations, chemotherapy, and irradiation, have been reviewed.[15] The current status can be summarized briefly.

Surgical resection is possible when there is a tumor or tumors involving only one lobe of a noncirrhotic liver, and when there are no metastatic lesions present at the time of the operation. In the United States, only 10 percent to 30 percent of patients with hepatocellular carcinoma are found to have resectable tumors at the time of such a procedure. The operative mortality is high. Dr. Robert Lim of San Francisco General Hospital (personal conversation, 1980) reported a patient who has survived eight years after an hepatic lobectomy for a large lesion of the right lobe. Generally, however, surgical therapy is likely to have limited impact on this disease. The surgical team at the University of Colorado had attempted but now has abandoned hepatic transplantation for HCC.

Initial results with radiation therapy have been similarly dismal. Radiation hepatitis is a major hazard, and the survival rate of patients treated with primary radiation seems to be no better than that of patients receiving no treatment. Systemic or regional chemotherapy with several different agents has been studied. The only agent that seems to have had an effect has been doxorubicin hydrochloride (Adriamycin), and this is being studied further. Friedman and co-workers[16] have reported early results obtained by combining intra-arterial chemotherapy directly into the liver with radiation therapy in 13 patients with hepatocellular carcinoma. There was symptomatic improvement in nine of eleven symptomatic patients, objective regression of tumor in six and no progression of the tumor in another five patients. In two patients there was no response at all. The survival of responders was a median of five months, and the side effects were considered "acceptable." There was some nausea and vomiting, and there were no catheter-associated side effects.

A hepatitis B vaccine has been developed after several years of investigation, and is being subjected to field trials in this country and elsewhere. The development of a hepatitis B vaccine holds out the greatest hope for the prevention of HCC.

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Important Advances in Clinical Medicine

Epitomes of Progress—General and Family Practice

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general and family practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in general and family practice which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Nitrates in Treatment of Congestive Heart Failure

CARDIAC FUNCTIONING is regulated by four factors: preload (ventricular end-diastolic volume), afterload (ventricular systolic thrust), contractility (force of ventricular contraction) and heart rate. These factors determine the stroke volume and cardiac output.

Consequently, the physiological approach to treatment of refractory heart failure is based on improving one or all of the above factors. In simple terms, preload, afterload, contractility and heart rate are corrected to allow the failing contractile force to discharge a normal cardiac output.

It has been known for some time that vasodilators such as parenterally given phentolamine (Regitine), sodium nitroprusside, and hydralazine, to various degrees, reduce both left ventricular preload and afterload, thereby decreasing pulmonary venous pressure and increasing cardiac output.

Only recently have nonparenteral medications such as topically administered nitroglycerin and orally administered isosorbide dinitrate been shown to reduce primarily the preload. Contrary to the action of parenterally given vasodilators, the nitrates appear to have more effect on venous volume than on the resistance vessels. Consequently, their action results in a greater reduction in left ventricular preload than in afterload, which, in turn, generally produces a reduction in left ventricular filling pressure and relieves symptoms of pulmonary congestion. The effects of nitrates on peripheral resistance and cardiac output are variable. These drugs are used primarily in treating patients with congestive heart failure and a high pulmonary capillary wedge pressure, but in whom the left ventricle maintains a normal cardiac output.

Nitroglycerin, given as a topical ointment in 1-inch strips, is effective for up to four hours. This amount may be increased by one inch every other day as needed. Isosorbide, administered orally or sublingually, is effective for up to three hours.

Another effect of nitrates which may improve the hemodynamics of the heart is the increase in myocardial oxygen supply. Many hypertrophied heart muscles need extra oxygen. Myocardial perfusion may be improved by the resulting dilatation of coronary arteries; however, the aortic

pressure should not be allowed to fall below that necessary to perfuse those same arteries.

But in patients with severe cardiac failure, in whom impedance (afterload) is a major factor in the failure, orally given hydralazine tends to decrease systemic vascular resistance. Afterload reduction should not be attempted, however, without determining the degree of pulmonary congestion and of peripheral hypoperfusion, while the patient is in the coronary unit.

It is remarkable how quickly systemic vasodilators have become an important new medical advance in the treatment of acute and chronic congestive heart failure. In the future, as more experience is gained with the use of nitrates and as newer vasodilators become available, these medications will likely be used as often as digitalis in the standard treatment of congestive heart failure. For the present, family physicians should use the nitrates only as a supplement to the standard regimen of digitalis, diuretics and decreased use of dietary salt.

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Fetal Monitoring

THE USE OF the nonstress test is a reliable indication of fetal well-being in cases of suspected uteroplacental insufficiency. The test is rapid and inexpensive, requires little physician time and is easy to carry out. It can be used in broader circumstances than the contraction stress test. The technique involves monitoring fetal heart rate and fetal activity. A reactive pattern consists of four episodes of an increase of fetal heart rate of at least 15 beats per minute, lasting 15 to 20 seconds after fetal movement. Twenty minutes are allowed for activity. If the activity does not occur, an additional 20-minute period is allowed.

A response other than full reactive, including (1) no fetal activity of fewer than four accelerations or (2) less than 15 beats per minute increase, demands further evaluation. A reactive pattern correlates well with fetal well-being and is equivalent to a negative contraction stress test. In situations requiring prolonged evaluation the test should be repeated weekly.

In a large study 75.5 percent of fetuses considered at high risk had reactive nonstress tests and went to term with no perinatal mortality. In conjunction with the contraction stress test, the nonstress test offers broader application, less expense and an accurate and sensitive screening program.

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Adjunctive Laboratory Tests for the Early Diagnosis of Pregnancy

CURRENTLY AVAILABLE IMMUNOLOGIC TESTS for pregnancy are based on detecting human chorionic gonadotropin (HCG) in the urine or blood. HCG is essential for the maintenance of the corpus luteum and the viability of early pregnancy.

HCG can reliably be detected in the urine by the antigen antibody reaction two weeks following a missed menstrual period, using the office slide test or the more sensitive two-hour laboratory tube test.

With radioimmunoassay (RIA), the β subunit of the HCG molecule can be detected shortly after implantation, several days before the missed period. This test is carried out using blood rather than urine and is extremely sensitive. Considerations limiting its use include, expense ($20 to $25) and the 36 to 48 hours required to obtain a result.

More recently available is the radioreceptor assay (RAA) test for HCG. This method detects the HCG molecule by measuring its competition for specific receptor sites on cell membranes prepared from bovine corpora lutea. Except for the potentially false-positive result due to the midcycle surge of luteotropin, also called luteotropic hormone (LH), at ovulation, this is the most sensitive test for pregnancy available. A test result can be provided in one to two hours, and the cost is $15 to $18.

HCG is essential for the maintenance of pregnancy and the amount present is generally proportional to the amount of trophoblastic tissue present. Significantly elevated levels may suggest multiple gestation, while very low levels may suggest impending abortion or a nonviable pregnancy. Absolute levels of HCG are useful in the diagnosis and monitoring of a hydatidiform mole and choriocarcinoma. These values are obtained

most reliably with the β subunit test, using the RIA method.

In addition to the normal trophoblast of pregnancy, both trophoblastic and nontrophoblastic neoplasms are known to be associated with elevated HCG levels as well.

WALTER P. ORDELHEIDE, MD

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New Concepts in the Treatment of Vaginitis

VAGINITIS CAN BE a frustrating problem for patients and physicians alike. In the past, the office procedure included the following steps: take a cervical culture for gonorrhea; look at a wet mount of the secretions for trichomonads, and then add sodium hydroxide to the secretions and look for mycelia, which would indicate an infection caused by *Candida*. When these tests were negative the infection was classified as nonspecific, and a variety of treatments were instituted. The main treatment for *Trichomonas vaginalis* was metronidazole (Flagyl) therapy, 250 mg three times a day for ten days, for both the patient and her sexual partner. Patients with candidal infections were treated with nystatin; patients with nonspecific vaginitis were treated first with a triple sulfa cream, followed by ampicillin given orally if the local treatment proved ineffective.

Recent improvements in methods of treatment will make patients and physicians much more comfortable. Miconazole and clotrimazole are replacing other drugs as the treatments of choice for *Candida albicans*. The current recommended treatment is a seven-day regimen of miconazole cream or clotrimazole tablets. Of course, patients who have recurrent candidal infections should be screened for diabetes mellitus. Also, administration of tetracyclines and birth control pills predispose women to candidal infections.

At present, shorter courses of Flagyl have been recommended for trichomonal infections. A regimen of 500 mg, taken twice a day for five days by both sexual partners, seems to be as effective as the ten-day course.

The most important new information on this subject has been written by Pheifer and coworkers. They studied patients with nonspecific vaginitis by cultures and determined that the usual treatment of *Haemophilus vaginalis* infections with sulfonamides and ampicillin was either useless or minimally effective. They advocate metroniazole (Flagyl) therapy for this problem, in a dosage of 500 mg two times a day for seven days. Also, *H vaginalis* can be identified sometimes by the presence of "clue cells" on Gram stains of specimens of the vaginal secretions. Addition of a 10 percent solution of potassium hydroxide to the wet mount will produce a fishy odor from the secretions of patients with *H vaginalis*.

With this recent information, patients with vaginitis stand a better chance of having their infections properly diagnosed and treated. This, in turn, should reduce the frustration of having these patients return to the office with continued symptoms because the treatment has proved ineffective.

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Positive End-Expiratory Pressure

POSITIVE END-EXPIRATORY PRESSURE (PEEP) has been available since 1967 as an adjunct to the management of adult respiratory distress syndrome. PEEP is the artificial maintenance of variable levels of positive pressure on expiration and the stopping of the flow of expired air at a pressure above atmospheric. This has become clinically feasible in most well-equipped hospitals because of the wide availability of volume respirators.

Increasing the interalveolar pressure at the end of expiration has deleterious effects on a normal person—the least of which is interference with normal pulmonary circulation, and the worst of which is causing pulmonary rupture. Fortunately, the type of condition in which PEEP is indicated is accompanied by a substantial decrease in lung compliance, and mechanical increase of expiratory alveolar pressure is safe and effective in increasing lung volumes and gas transfer, without major risk of transmission of pressure to pleura and blood vessels.

PEEP is indicated for a patient who has refractory hypoxemia unresponsive to increasing the fraction of inspired oxygen (FIO_2). Oxygen toxicity is frequent with an FIO_2 above 60 percent and

the percentage saturation of hemoglobin begins to fall precipitously below an arterial oxygen pressure (Pa_{O_2}) of 60 mm of mercury. Therefore, a patient may be considered to manifest refractory hypoxemia if the Pa_{O_2} remains below 60 mm of mercury while breathing 60 percent FIO_2; in this situation, PEEP should be considered.

PEEP is felt to improve gas exchange by expanding collapsed alveoli, and there is in each patient a level of PEEP which will prove effective in accomplishing this end. PEEP, therefore, should be increased incrementally, usually by steps of 5 cm of water, monitoring arterial gases until there is an increase in Pa_{O_2}, or until clinical deterioration occurs. An optimal level of PEEP is usually associated with a dramatic improvement of the Pa_{O_2} as well as sequential improvement in the pulmonary compliance which can be measured at the bedside.

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The Health Hazard Appraisal

OVER THE PAST 15 years, the Health Hazard Appraisal has developed from an idea held by Dr. Jack Hall and other clinicians at Methodist Hospital in Indianapolis to a recognized and accepted tool for use by primary care physicians in their practices. The Health Hazard Appraisal uses data on mortality to assist the physician and patient in identifying those factors in a patient's life-style, such as health habits, which have a predictable negative influence on his or her expected length of life. By identifying these risk factors a physician is able to counsel a patient about their predicted effects. In addition, the Health Hazard Appraisal is able to identify and suggest certain achievable changes in the patient's habits to effect a positive change in his or her predicted risk of death or, alternatively, expected length of life.

The Health Hazard Appraisal is initiated by a physician by the completion of a data sheet. This data sheet couples a self-administered history by the patient with certain objective information supplied by the physician, such as blood pressure, weight and level of serum cholesterol. This information is then mailed to one of the Health Hazard Appraisal Centers which submits it to computer analysis. A complete report is returned to the physician for his or her use. The cost varies, depending on which referral center is used, but approximates $10 to $20 per appraisal.

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Treating Homosexual Patients

THERE IS A growing tendency to recognize a special galaxy of knowledge necessary for treating homosexual patients. Homosexual medicine is an important new area recognizing that knowledge of homosexual men and women and their sexual practices and eventual diseases is necessary to properly serve a patient population that is emerging from "the closet" and demanding a more candid relationship with their physicians. So, there is an importance now of being aware of homosexual patients and their "families"—whether a group of friends or a sexually monogamous lover of many years.

Homosexual men and women are as diverse as the population in general—nevertheless, the difference in their sexual preference results in greater vulnerability to sexually transmitted diseases.

Hepatitis B is fast becoming a venereal infection with relatively high morbidity rates and without effective treatments. The disease, which used to be thought of as being caused by hypodermic punctures or blood transfusions, is now more frequently found to be caused by sexual contact. In some studies, up to 90 percent of hepatitis diagnosed in the homosexual population is positive for hepatitis-associated antigens. Also of note is the incidence of hepatitis B surface antibody that is significantly higher in this population, up to 15 percent in some studies.

There has been increasing knowledge gained on another disease related to this population: condylomata accuminata (venereal warts). This is a disease with no effective single therapy except patience and persistence.

The best single help for homosexual patients is education and, in particular, alerting them to an awareness of their bodies, especially self-examinations for early detection of condylomata.

One hallmark of effective condylomata treatment is discovery and early eradication, usually by fulguration. Early detection can be accomplished by frequent, if not daily, self-administered

rectal examinations while showering. In the author's practice, this suggestion to homosexual patients has proved to be a highly effective means of accurate discovery of the existence and location of condylomata, or of a recurrence following original treatment.

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The Use of the Oxytocin Challenge Test in High-Risk Pregnancies

THE OXYTOCIN CHALLENGE TEST (OCT; also called the contraction stress test) is an attempt to duplicate the stresses of labor by inducing contractions and observing the fetal heart response. This test has been widely accepted in the United States as a useful clinical method of assessing fetal well-being in the hazardous intrauterine environment encountered in certain high-risk pregnancies.

The test consists of intravenous administration of oxytocin by an infusion pump sufficient to produce three contractions during a ten-minute interval, and the simultaneous recording of fetal heart rate and uterine contractions using an electronic fetal monitor. When clinically indicated, the test can be carried out as early as in the 32nd week. The test can be done without oxytocin when contractions are occurring spontaneously.

This test is contraindicated in cases of suspected labor before term, vaginal bleeding and cervical incompetence. Relative contraindications include previous cesarean sections or multiple gestation when a premature fetus would compound the survival risk factor.

A positive test result is determined by a fetal monitor recording of late or variable decelerations of fetal heart rate at, or just beyond, a uterine contraction. The pattern should be repeated with most subsequent uterine contractions or with each of three contractions with an interpretable heart rate during a ten-minute period. Positive findings, if not acted on, are associated with a high incidence of fetal death or fetal distress.

A negative test finding is clearly the greatest benefit of the OCT and is observed in about 90 percent of cases. A negative response is interpreted when uterine contractions occur at a frequency of three in ten minutes with no decelerations of fetal heart rate. To maintain surveillance on the uterofetal-placenta unit, a negative test may be repeated at intervals of a week or less.

A suspicious result is shown by definite, but inconsistent, late decelerations failing to persist with most uterine contractions. After a suspicious test result, it is advisable to repeat the test in 24 hours.

The test is considered unsatisfactory if the quality of the recording is technically poor enough to prevent determining whether decelerations are present, or if there are fewer than three contractions in ten minutes.

The test requires 90 to 120 minutes and should be done with meticulous care by trained nursing and medical personnel.

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Parathyroid Hormone and Calcium Abnormalities

THE GREATER AVAILABILITY of laboratory analyses of chemical fractions of the blood of patients seen by family physicians has made it possible to diagnose hypercalcemia in patients who may not have presented with the clinical features of primary hyperparathyroidism. The parathyroid hormone (PTH) assay is also available and may be added to the battery of tests used in the evaluation of clinical problems.

The specificity of the parathyroid hormone analysis is sufficient to recognize fragments and intact PTH. However, in some 15 percent to 20 percent of patients there is sufficient overlap, in which it is possible to have high PTH production without primary hypothyroid adenoma, parathyroid hyperplasia or parathyroid carcinoma. The source of the ectopic production of the parathyroid hormone in these cases is usually a malignant lesion. The changes noted in hyperparathyroidism, notably hypercalcemia, hypophosphatemia and elevated levels of alkaline phosphatase, as well as the clinical symptoms of debilitation or constitutional signs of a malignant condition, may be extremely important in differentiating the

source of elevated PTH. Generally, patients with malignant lesions tend to have higher levels of serum calcium than patients with primary hyperparathyroidism; the PTH levels are lower in patients with malignant lesions in contrast to levels noted in patients with primary hyperparathyroidism; and high levels of calcium, are attained more rapidly than in the chronic and slowly progressive disorder that marks primary hyperparathyroidism.

In the differential diagnosis of hyperparathyroidism, other sources of hypercalcemia need to be considered. These may include, in addition to neoplasms with or without metastasis, multiple myeloma, sarcoidosis, thyrotoxicosis, immobilization in the young, Paget disease, vitamin D intoxication, milk-alkali syndrome, Addison disease and the use of thiazide diuretics.

A workup by physicians in family practice for a patient who has hypercalcemia should include a careful history; complete blood count; studies of sedimentation rate, electrolytes (including serum), magnesium levels, protein electrophoresis and thyroid function; x-ray study of the chest; an intravenous pyelogram, and skeletal survey x-ray studies. When the association among hypercalcemia and hypophosphatemia and increased alkaline phosphatase is noted, and confirmed on repeated examinations, the immunoassay test for parathyroid hormone may be indicated. Additional tests which may be useful include measurement of tubular absorption of phosphate after either calcium or phosphate infusion.

If serum calcium levels are greater than 15 mg per dl hypercalcemia is severe. When the patient is symptomatic, a short QT interval may be noted on the electrocardiogram, and this requires restricted calcium intake, hydration, forced diuresis with furosemide and ethacrynic acid. In long-term management, therapy with steroids may be indicated as well as oral administration of phosphates. Dialysis may be considered in a life-threatening situation in which the use of other measures is restricted. Mithramycin inhibits bone resorption and lowers the calcium level when given intravenously in a dose of 25 mg per kg of body weight.

Patients who have increased calcium levels and no evidence of clinical disease should be observed closely for the development of clinical or chemical abnormalities that may indicate progression of hyperparathyroidism.

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EDITORIALS

The Medicaid Dilemma

TWO ARTICLES ELSEWHERE in this issue draw attention to the Medicaid (known in California as Medi-Cal) dilemma, a dilemma which so far has defied solution anywhere. Noble in concept and endorsed by the medical profession (at least in California) the Title XIX program was to provide "mainstream" medical care for the poor through a combination of federal and state funds. In spite of many difficulties, including a totally inadequate fee structure for physicians, the medical profession in California has continued to support this program and has even gone to court successfully in behalf of its beneficiaries.

In contrast to the Title XVIII Medicare program, which to a large extent was shaped through national debate over a period of years, Title XIX was passed by Congress almost as an afterthought, a "frosting on the cake," with a minimum of discussion about how it might operate or what might be its long-range implications. Perhaps as a consequence, Medicare has worked fairly smoothly in actual practice while Medicaid has been plagued with unforeseen problems which have yet to find satisfactory solution.

In California the thought was that if the state Medicaid program was to be done at all, it should be done right, with the poor being given genuine access to mainstream medical care and eliminating charity on the part of both physicians and hospitals which at that time had come to be described as demeaning. The result was that California established one of the most generous Medicaid programs in the nation with the full support of the California Medical Association which continues to believe that mainstream care for all is equitable and right.

The unforeseen problems which have developed are described by Myers and Leighton and by Heckman and Jones in this issue. Medical science has made mainstream care more effective and more costly whether for rich or poor. The ravages of inflation affect the value of government dollars for medical care as much as anyone else's. They buy less care for the same number of dollars, or they buy the same care for more dollars. Over the years the eligibility requirements in California for Medi-Cal have been modified until now 13 percent of the population of the state has entitlement. And it has been proved that restricting what is paid to physicians and bleating about fraud contribute little to solving the fundamental dilemma. The state of California is now putting its money on and into computerized billing, using an optical scanner billing form which will gather a great deal of information about services rendered as well as pay bills. So far this appears to be creating more problems than it is solving, and it certainly adds to the cost of the providers who are trying to give mainstream care to the beneficiaries of this program, often at a cost greater than the payments they may or may not receive for doing so.

The Medicaid dilemma is real enough—in California at least. More has been bitten off than can be readily chewed, let alone swallowed, digested or absorbed. Tension, stress and confrontation between government and the health care enterprise have been the order of the day almost since the inception of the program. All this confrontation has not been particularly useful or productive. Yet it is likely that all concerned would truly like to see all Californians have access to the same quality and quantity of medical care, which by definition would be mainstream care. If this is true, then one would hope that all parties with genuine interest might at some time get together, face up to the problems and agree on precisely what they are; agree on who needs to

do what about them; and then do what all will have agreed must be done. The disordered approach of the last decade or more simply has not worked well, nor is it likely that it ever will.

—MSMW

Evaluation of Asymptomatic Patients

PERIODIC HEALTH EXAMINATIONS (PHE's) are carried out in asymptomatic patients in an effort to prevent disease or to identify it at a very early stage. These encounters have contributed to a more complete patient data base and have facilitated physician-patient rapport, factors identified with improved patient care. A large, prospective study showed that death rates from certain "potentially postponable" disorders—such as hypertension and carcinoma of the colon—are reduced in those receiving PHE's.[1] Nonetheless, opponents have charged that the purported benefits of PHE's are not supported by firm scientific data.

Two recent reports provide PHE guidelines and shed light on the aforementioned criticism. An American Cancer Society report details recommendations for a "cancer-related checkup."[2,3] The report of the Canadian Task Force on the Periodic Health Examination[4] reviews the effectiveness of prevention and treatment of 78 conditions and lists recommendations based on sex, age and risk category.

In general, the recommendations point toward a "streamlined" PHE. For example, the American Cancer Society now advises that women over the age of 20, and those under 20 who are sexually active, have a Pap test "at least every three years, but only after they have had two negative Pap tests a year apart." The same report no longer recommends annual x-ray studies of the chest for the detection of lung cancer.

It should be noted that both reports have stirred controversy. Critics have observed that the guideline for x-ray studies of the chest is premature and in part based on preliminary data from ongoing prospective studies. The report of the Canadian Task Force does not recommend a "complete history and physical examination." This report refers to the studies on which its recommendations are based. For many crucial questions it is noteworthy that pertinent data are not available; hence the recommendations are often merely a summary of "expert opinion."

While physicians may take issue with specific recommendations, these reports merit careful study. Individual practitioners can then formulate PHE guidelines that are best suited for their patients. This will contribute to improved care and more efficient use of the health care dollar.

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Adenomatous Colonic Polyposis: To Lump or to Split?

WITH AN INCIDENCE of about one per 8,000 population, the familial polyposis disorders occur often enough that most physicians will encounter affected persons sometime during their practicing lifetimes. Whether these persons and their relatives are properly managed depends on a physician's familiarity with the manifestations of these disorders as well as with the genetic implications. Because several of these disorders predispose to carcinoma of the colon and rectum, the death of a patient or relative from cancer that might have been prevented at these sites represents a failure of medical care whether due to factors controllable by the patient, the physician or both.

Most of these disorders follow an autosomal dominant inheritance pattern so that they are not uniformly distributed in the population but are clustered in families. Recognition and proper diagnosis are hindered by poor history-taking, the preponderance of internal manifestations and the great variation of symptoms among affected persons, even among members of the same family.

Why genetic disorders involving autosomal dominant inheritance are so variable in their outward manifestations is by no means clear. This lack of understanding, however, is likely to persist because only about six disorders have been characterized at the molecular level. At present these clinical disorders are difficult to study quantitatively because of technical limitations on the nature, frequency and extent of methods of examining the largely internal structural changes.

Another factor contributing to the uncertainty and confusion among physicians in differentiating these disorders is the inclination of many investigators to "lump" them diagnostically despite possible distinguishing features that suggest genetic heterogeneity. A more appropriate approach is given in the article by Gardner and colleagues elsewhere in this issue. They discuss the most recent results of studies initiated by Dr. Gardner over 30 years ago.

Familial polyposis coli (FPC) has been known since the last century, but investigation of the Gardner syndrome (GS) as a separate entity began in 1947. Both segregate in an autosomal dominant pattern, vary substantially in the age of persons at onset, and are characterized by the presence of adenomatous polyps and a strong predisposition to adenocarcinoma of the colorectum. What, then, are the real differences between GS and FPC? Indeed, what is the evidence that they are really distinct and separate disorders? Some have proposed that FPC and GS represent points on a single spectrum, possibly at a single gene locus, and have even suggested logical but currently untestable genetic mechanisms to account for the observed variation. The evidence, however, still appears to weigh heavily in favor of their distinctiveness.

The distribution and numbers of adenomatous polyps are possible differentiating points. Although involvement in FPC had been thought to be limited to the colon and rectum, more recent evidence, especially from fiberoptic endoscopic studies, indicates that polyposis can occur in any portion of the gastrointestinal tract. Attention is focused justifiably on the colorectum because of the much greater tendency for adenocarcinoma to develop there.

McKusick[1] suggested that the colonic polyps in GS were fewer in number and more scattered than in familial polyposis coli. Bussey,[2] however, in describing the large number of patients in the St. Mark's Hospital Polyposis Register, found a wide range in number and distribution of polyps in colectomy specimens from FPC and GS patients, thus providing little support for the McKusick hypothesis. On the other hand, Gardner and colleagues conclude that their observations support the hypothesis.

Questions must be raised, however, about the roles of extracolonic manifestations of GS and of surgical intervention as possible confounding factors. It is clear from kindred 109 and other families that some GS patients have extragastrointestinal manifestations for years before colorectal polyps are detected. These largely external abnormalities could be signals leading to earlier diagnosis, especially in relatives of an affected patient. Hence, colectomy would be more likely to be carried out at an early stage when fewer, more scattered polyps are present. These possibilities are at least consistent with the observations. It is unfortunate that the observed difference is not the other way around, with FPC having fewer, more scattered polyps than GS, because then the tendency toward biased ascertainment would seem less likely to interfere.

Gardner and associates, as well as many other authors, feel that the extragastrointestinal lesions are the more distinctive features. Yet, as indicated by Bussey,[2] the harder that investigators look to find these characteristic GS lesions, the more likely they seem to be found in patients diagnosed as having FPC. This seems to be most true for osteomas, and least true of desmoid tumors as judged by the more recent literature. At the very least, these occurrences suggest that based on present diagnostic criteria, it may not be possible to distinguish between GS and FPC in some families, and that errors are made regularly. Regrettably, this situation is made worse by those authors who neither attempt to test possible distinctions nor clearly warn their readers that they are "lumpers" rather than "splitters."

One way out of this diagnostic quandary would be to identify in vitro one or more precisely measurable features that distinguish between the GS and FPC genes, assuming of course that they differ. Studies of growth characteristics of cultured skin fibroblasts, ploidy (multiples of the hormonal number of chromosomes) in cultured adenoma epithelial cells and cell kinetics in adenomas are so demanding technically that any putative distinctions identified would need confirmation in more than one laboratory.

A marker that is closer to the gene will be

necessary. The large and readily available kindreds as discussed by Gardner and colleagues could provide fertile ground for the application of recombinant DNA techniques in order to find, for example, a restriction enzyme cleavage site that is tightly linked to either the GS or FPC gene, but not to both. To date this has only been possible in the case of sickle cell anemia[3]; however, studies now in progress seem likely to yield other such instances. Or perhaps the critical distinctions are within the gene itself, with the recombinant DNA techniques yielding surprising insights into mutation in humans as has recently been found in one form of thalassemia.[4] If such an approach becomes feasible with the polyposis disorders, then diagnoses could be made at any age, using DNA from any nucleated cell—leukocytes and skin fibroblasts being convenient sources—and independent of the presence or absence of any manifestation of the genes. Until then we will need to be as careful as we can be in assessing and quantitating the differentiating features so nicely presented here in the article by Gardner and colleagues.

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CASE REPORTS

Refer to: McLeod R, Smith S, Poore TE, et al: Tubo-ovarian actinomycosis and the use of intrauterine devices. West J Med 132:531-535, Jun 1980

Tubo-ovarian Actinomycosis and the Use of Intrauterine Devices

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ACTINOMYCOSIS, a chronic suppurative disease caused by an anaerobic actinomycete, most commonly involves the face, thorax or abdomen.[1] The pelvis is an unusual location for infection with actinomycetes. Twenty cases of pelvic actinomycosis associated with use of an intrauterine device (IUD) have been reported[2-10]; three were diagnosed by culture and histology, one by culture and histology of an accompanying subphrenic abscess and 17 by histology alone. We recently cared for a patient with IUD-associated pelvic actinomycosis, in which the organism was identified by histologic testing and culture. Because the number of women using IUD's is growing it is likely that more cases of this infection will occur. Thus, a review of methods of diagnosis and management of IUD-associated pelvic actinomycosis should be useful.

Report of a Case

A 29-year-old woman, gravida 2, para 1, had a therapeutic abortion in March 1971. She used an IUD (Dalkon Shield) from 1971 until April 1975, when it was removed because of menometrorrhagia. At the time of its removal, the physician observed that the IUD had been lying transversely. In June 1975 the patient noted pain in the lower left quadrant of her abdomen. A mass in the left ovary was palpated on pelvic examination. However, she refused further evaluation at that time.

In August 1976 the patient complained of continued abdominal pain. On physical examination she had a firm, slightly tender, 7-cm mass in the left adnexa, contiguous with the uterus. A physical examination showed no other abnormalities. There were 11,200 peripheral blood leukocytes

Figure 1.—Tubo-ovarian abscess, 5 by 2.5 cm.

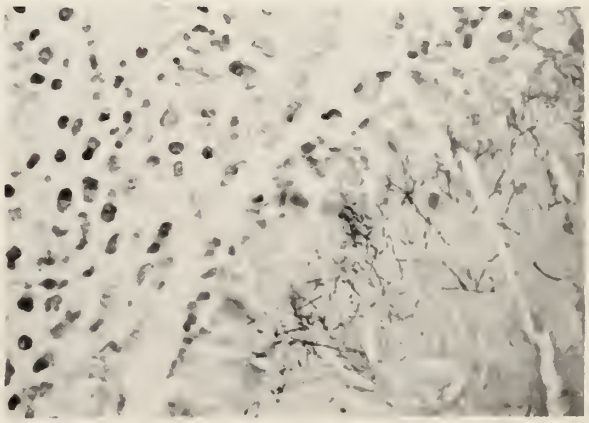

Figure 2.—Microscopic section of tubo-ovarian abscess. Gram-stained preparation with Gram-positive, filamentous, branching rods and acute and chronic inflammatory cells within a fibrous matrix.

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TABLE 1.—*Diagnosis, Treatment and Outcome of Therapy in 21 Patients With Endometrial or Tubo-ovarian Actinomycosis*

Case No.	Method of Diagnosis*	Site	Treatment: Antibiotic	Dose (grams/day)	Route	Duration	Surgical or Other Procedure	Outcome—Follow-up When Patient Reported Well (yrs)
1[2]	H(+),C(−)	Right	Penicillin	2.5	IM	about 8 days postop	TAH-BSO	2
			Penicillin	2	PO	6 months postop		
			Streptomycin	NA	NA	NA postop		
			Sulfisoxazole	4	PO	6 months postop		
2[3]	H(+),C(+)	Bilateral	Penicillin	3.75	IM	6 weeks postop	Bilateral excision of abscess followed by TAH (a year later)	2.75
3[3]	H(+)	Bilateral	Co-trimoxazole	4 tablets/day	PO	8 days preop	TAH-BSO	0.58
			Tetracycline	1	PO	8 days preop		
			Penicillin	1	PO	3 months postop		
4[4]	H(+),C(−)	Bilateral	Ampicillin	1	PO	3 days preop	TAH-BSO	1
			Penicillin	3.125	IV	1 dose during operation		
			Penicillin	9.375	IV	3 days postop		
			Penicillin	4	PO	5 days postop		
			Penicillin	2	PO	1 year postop		
			Kanamycin	1	IM	1 dose during operation		
			Kanamycin	1	IM	5 days postop		
5[5]	H(+),C(+)	Bilateral	Cephalothin	NA	NA	NA preop and postop	TAH-BSO	3
			Gentamicin	NA	NA	NA preop and postop		
			Clindamycin	NA	NA	3 weeks postop		
6[5]	H(+),C(+)†	Left	Ampicillin	NA	NA	NA preop	TAH-BSO	2
			Penicillin	NA	NA	NA postop		
			Clindamycin	NA	NA	NA postop		
			Penicillin	NA	PO	6 months postop		
7[6]	H(+)	Left	Penicillin	2	PO	30 days postop	TAH-BSO	0.67
8[7]	H(+),C(+)	Bilateral	Lincomycin	NA	Parenteral	NA postop	BSO	1
			Gentamicin	NA	Parenteral	NA postop		
			Penicillin	NA	Parenteral	NA postop		
			Penicillin	NA	PO	3 months postop		
9[8]	H(+),C(−)	Left	Penicillin	NA	NA	NA	TAH-BSO	NA
10[8]	H(+),C(−)	Bilateral	Penicillin	NA	NA	NA	TAH-BSO	NA
11[8]	H(+),C(−)	Endometrial	Erythromycin	NA	NA	NA	IUD removed	NA
12[8]	H(+),C(−)	Endometrial ? adnexal	Penicillin	NA	IV	20 days§	IUD removed	NA
			Kanamycin	NA	NA	NA		
13[8]	H(+),C(−)	Endometrial	Penicillin	NA	NA	NA	IUD removed	NA
14[8]	H(+),C(−)	Endometrial ? adnexal	Penicillin	NA	NA	NA	IUD removed	NA
16[8]	H(+),C(−)	Left	Penicillin	NA	NA	NA	TAH-BSO	NA
17[8]	H(+),C(−)	Endometrial ? adnexal	Ampicillin	NA	NA	NA	IUD removed	NA
18[8]	H(+),C(−)	Endometrial	Penicillin	NA	NA	NA	IUD removed	NA
19[9]	H(+)	Left	Penicillin	12.5	IV	2 weeks postop	TAH-BSO	0.75
			Clindamycin	0.6	PO	9 months postop		
20[10]	H(+),C(−)	Bilateral	Cephalothin	4	IV	7 days preop	TAH-BSO	3
			Kanamycin	1	IM	7 days preop		
			Chloramphenicol	3	IV	14 days preop		
			Chloramphenicol	2	IV	NA preop		
			Tetracycline	1.5	IV	14 days preop and postop		
			Tetracycline	2	PO	30 days postop		
21‡	H(+),C(+)	Bilateral	Penicillin	18.75	IV	2 days after 1st operation	Left salpingo-oophorectomy followed by TAH and right salpingo-oophorectomy (51 days later)	0.5
			Penicillin	2	PO	30 days after 1st operation		
			Gentamicin	0.24	IV	2 days after 1st operation		
			Penicillin	12.5	IV	10 days before 2nd operation		
			Penicillin	12.5	IV	7 days after 2nd operation		
			Penicillin	2	PO	14 days after 2nd operation		

IM=intramuscular; IUD=intrauterine device; IV=intravenous; NA=not available; PO=by mouth; postop=postoperatively; preop=preoperatively; TAH-BSO=total abdominal hysterectomy and bilateral salpingo-oophorectomy

*H(+)=*Actinomyces* identified in histologic preparation; C(+)=*Actinomyces* identified in culture; C(−)=*Actinomyces* not identified in culture.
†Subphrenic, not pelvic.
‡Present case.
§Time of administration unknown.

per cu mm with 73 percent polymorphonuclear cells and 6 percent band forms; the hematocrit was 30 percent and sedimentation rate was 59 mm per hour (Wintrobe). Vaginal culture and culdocentesis were not done. A laparotomy was carried out in August 1976, and a 5- by 2.5-cm tubo-ovarian abscess on the left side was found (Figure 1). Adhesions and clubbing of the right fallopian tube were also noted during the operation. The left ovary and fallopian tube were excised. Although inflammatory disease involving the right ovary and fallopian tube was evident, the right adnexa was left in place in accordance with the patient's preoperative request. Treatment consisted of 30 million units per day of aqueous penicillin given intravenously for two days, 80 mg of gentamicin given intravenously every eight hours for two days and 2 grams per day of penicillin V given orally for the following 30 days. Histologic examination of the excised tubo-ovarian abscess disclosed Gram-positive, filamentous, branching rods, with acute and chronic inflammatory cell infiltrates within a fibrous matrix (Figure 2). Culture of the tubo-ovarian abscess showed a pure growth of *Actinomyces israelii*.

At a subsequent clinic visit in September 1976, the patient felt mild lower abdominal pain on palpation of the right adnexal area; a pelvic examination and sonogram showed a mass in the right adnexa. The leukocyte count was 6,400 per cu mm, and sedimentation rate was 46 mm per hour (Wintrobe). She was admitted to hospital and treated with 21 million units of penicillin G given intravenously each day for 17 days (10 days before the operation and 7 days afterwards). In October a second laparotomy was done, and inflammation and fibrosis of the right adnexal area with adhesions and clubbing of the fallopian tube were noted. A 5-cm cyst involving the right ovary was noted, and the ovary, the right fallopian tube and the uterus were removed. Histologic examination and culture showed no evidence of actinomycetes in any of these tissues, although extensive acute and chronic salpingitis was noted. The patient was given 500 mg of penicillin orally four times per day for two weeks after discharge from the hospital. She was well six months after the second surgical procedure.

Comment

This case illustrates certain typical epidemiologic features of tubo-ovarian actinomycosis and

the problem of establishing a preoperative diagnosis.

It is often difficult to distinguish the clinical presentation of tubo-ovarian actinomycosis from that of chronic pelvic inflammatory disease caused by other organisms. As in the case reported above, pelvic actinomycosis usually presents as a chronic indolent disease with symptoms persisting from months to years. The average time from onset of symptoms to diagnosis in one series was 19 months.[11] In our patient, weight loss, lower abdominal and pelvic pain, and clinical course were more consistent with a pelvic tumor than with an acute infectious process.

Tubo-ovarian actinomycosis generally occurs in distinct clinical situations: following appendicitis or abdominal surgical procedures,[10,12] and in the presence of an IUD.[2-10] Actinomycosis is thought to occur in these circumstances because intestinal or uterine mucosal barriers are disrupted due to inflammation or mechanical trauma, thereby allowing colonization with *A israelii,* a species of bacteria normally present in humans in the vagina or gastrointestinal tract.[3,10,13] Recent reports have described organisms in histologic and cytologic preparations of smears, stained with Gram and acid-fast stains, from the genital tract of women who have used IUD's.[14] Data concerning identification of the organism by culture, however, have not been provided.

The specific location of pelvic actinomycosis appears to depend on predisposing factors. For example, tubo-ovarian actinomycosis described in the earlier literature occurred on the right side in 38 percent of cases, on the left side in 18 percent and bilaterally in 44 percent.[11] The predominance of disease on the right side over the left was attributed to earlier appendicitis or appendectomy in many cases. In our review of the 21 cases of IUD-associated pelvic actinomycosis (20 previously reported cases and the present case), 7 patients had endometrial infections documented by histologic examination alone. Of the remaining 14 cases, the lesions were on the right side in 7 percent (one of 14), on the left side in 36 percent (five of 14), and bilateral in 57 percent (eight of 14) (Table 1). Although the number of cases is small, there are more cases of IUD-associated pelvic actinomycosis on the left side than in earlier series[4,11] in which the development of disease was thought to be related to previous appendiceal disease.

Diagnosis of actinomycosis is generally based on histologic evidence of classic sulfur granules and Gram-positive, nonacid-fast, branching, filamentous bacteria (Figure 2 and Table 1). Cultures are frequently negative, possibly because the organism is fastidious or because anaerobic specimens are often handled improperly. Because the organism may be difficult to culture and other organisms may produce similar histologic features,[15] additional diagnostic techniques have been developed.

A serologic test that assays for precipitating antibody to actinomycetes by counterimmunoelectrophoresis is being evaluated to diagnose actinomycosis; thus far, it has been reported to be sensitive and specific.[16] Presence of antibody, measured by this assay, is reported to persist for six months in the absence of exacerbations of actinomycosis.

A fluorescent antibody technique has been reported to be useful in identifying actinomycetes in tissue.[17] In a recent study, 36 women had evidence of actinomycetes in Papanicolaou-stained cervicovaginal smears; 9,191 smears were analyzed.[18] Actinomycetes were identified exclusively in patients wearing an intrauterine device or vaginal foreign body (IUD's and pessaries). By using fluorescein isothiocyanate-labeled antiserum, the organisms were shown to be *A israelii* in eight randomly selected smears. Nine of the 36 patients (25 percent) had pelvic inflammatory disease, a rate that appears to be much higher than the already high rate among all IUD users. The authors of the report concluded that this observation underscored the importance and clinical significance of finding actinomycetes in the vaginal smears of IUD users and that Papanicolaou-stained cervicovaginal smears provided a relatively easy, inexpensive, fast and highly specific method for the morphologic diagnosis of actinomycetes. They also suggested that these smears permit recognition, at a relatively early stage, of a group of patients who are potentially at risk for the development of pelvic inflammatory disease and its associated more severe complications.

In an attempt to establish guidelines for treating our patient, we reviewed the available literature (Table 1). Removal of the IUD and administration of 8 million units of penicillin G over two weeks (personal communication, M. A. Schiffer, January 1979) probably constitutes adequate treatment of endometritis caused by actinomycetes.[8] All cases of IUD-associated tubo-ovarian

abscess reported in the literature have been treated by abdominal hysterectomy, salpingo-oophorectomy and, in addition, administration of penicillin or a cephalosporin (Table 1, patient 5). The mode of administration and the dose of penicillin given have varied widely. The smallest dose of penicillin given to any patient was 1 gram per day of penicillin V for three months; this patient was reported to be well seven months after therapy began.[3] It is noteworthy that one patient with tubo-ovarian actinomycosis secondary to appendicitis was treated with a total of 86.8 million units of penicillin over approximately three months and a total of 9.5 grams of sulfadiazine, and subsequently had a normal pregnancy and delivery.[12] Data derived from in vitro sensitivity testing as well as treatment of actinomycosis in other sites[19-21] provide evidence that erythromycin, tetracyclines and clindamycin, as well as cephalothin and chloramphenicol, are reasonable alternative drugs for treatment of tubo-ovarian actinomycosis in patients who are allergic to penicillin.

Summary

Tubo-ovarian actinomycosis was diagnosed in a woman who had been using an IUD. The organism was identified by histologic analysis and culture. This case and 20 previously reported cases of IUD-associated pelvic actinomycosis are reviewed. Methods of diagnosis and management are emphasized because this infection is more likely to occur in view of the increasing use of IUD's.

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Post-*Yersinia* Arthritis

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REACTIVE ARTHRITIS is the term used at present for a sterile arthritis following infection in a part of the body that is remote from the joints.[1-4] Reiter syndrome is an example. The arthritis is usually of abrupt onset, involves relatively few joints and, characteristically, occurs after a latent period of a few days to two or three weeks. The antecedent infections are bacterial or chlamydial. By custom, the term excludes viral-associated arthritides. This report describes the cases of four patients in Northern California with arthritis following gastroenteritis caused by *Yersinia enterocolitica*. This syndrome was first described by Ahvonen and colleagues[1] in a report of 11 patients in Finland with erythema nodosum, including arthritis in two patients, following *Yersinia* enteritis. A similar syndrome may be associated

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ABBREVIATIONS USED IN TEXT

ANA = antinuclear antibody
ESR = erythrocyte sedimentation rate
LF = latex fixation
PMN = polymorphonuclear

with diarrheal disease due to *Salmonella*[2] or *Shigella*.[3] Aho and associates[4] noted the presence of the HLA-B27 histocompatibility antigen in 43 of 49 patients with reactive arthritis following *Yersinia* infection, as compared with 3 of 20 patients who had *Yersinia* enteritis without arthritis. In the normal Finnish population the prevalence of the HLA-B27 antigen is 14 percent. Studies of patients with reactive arthritis following *Salmonella*[5] and *Shigella*[3] infections have shown the same relationship to the HLA-B27 antigen.

Reports of Cases

CASE 1. In an 11-year-old girl from a dairy farm in Sonoma County, California, diarrhea developed in October 1977; it lasted for ten days and was never bloody. She lost 10 pounds. No enteric bacterial pathogens were recovered on stool culture, and one stool examination was negative for ova and parasites. Twelve days following the onset of diarrhea, pain in one hip developed, sufficient to make her limp. Two days later swelling and pain developed in the right wrist, followed within a few hours by pain and swelling of both ankles and over the dorsal surfaces of both feet. No other abnormalities were present on physical examination, and the girl remained afebrile. The leukocyte count was 12,400 per cu mm, with a differential of 71 percent polymorphonuclear (PMN) leukocytes, 2 percent banded forms, 20 percent lymphocytes, 5 percent monocytes, 1 percent eosinophils and 1 percent basophils. Hemoglobin was 11.8 grams per dl and the hematocrit was 33.9 percent. The erythrocyte sedimentation rate (ESR) was 58 mm per hour. The platelet count was 690,000 per cu mm. Findings of the latex fixation (LF) and antinuclear antibody (ANA) tests, analysis of the urine and a test for the hepatitis B surface antigen (HBsAg) were all negative. There were no significant titers of antibodies against *Salmonella* somatic antigen of types A, B, D or E, or against *Brucella*. The test for HLA-B27 antigen was positive, and a serologic titer for antibodies against the intestinal pathogen *Yersinia enterocolitica* (type 21 antigen) was positive in a dilution of 1:320. Treatment with acetylsalicylic acid, 0.6 gram four times per day, was begun, and later the dosage was increased to 0.9 gram four times per day. On this latter dosage, with a salicylate level of 29 mg per dl, the serum glutamic oxaloacetic transaminase (SGOT) level reached 143 IU per liter. The acetylsalicylic acid dosage was reduced to 0.6 gram three times a day. The arthritis improved gradually, but progressively, over six months, and she has remained asymptomatic since that time. In this case there has never been clinical or roentgenographic evidence of sacroiliitis.

CASE 2. A 13-year-old boy from Santa Clara County, California, vacationed with his family on the Sacramento River Delta in August 1978, where he swam in the river and drank well water and milk from local dairy farms. On September 10, 1978, fever, sore throat and slight cramps developed in the boy. A throat culture was negative for *Streptococcus*, and he improved in two or three days. On October 4 a high temperature, to 39.4°C (103°F), recurred and lasted for five weeks. The fever was accompanied by nonbloody diarrhea with up to eight stools per day. This continued for four days, and was followed by pain in the boy's thighs, ankles and the right hip. Only a moderate conjunctivitis was found on physical examination. Pain occurred in the left hip the next day, but all pain improved with treatment with acetylsalicylic acid, in a dosage of 0.6 gram, three times a day. The complete blood count showed no abnormalities, other than a minimal leukocytosis with a slight increase in banded polymorphonuclear leukocytes. The ESR was 56 mm per hour; the antistreptolysin titer was 125 Todd units and the LF and ANA tests were negative. A tine test and a coccidioidin skin test were both negative as well. On the tenth day of fever, and five days after diarrhea had ceased, an erythematous, indurated rash "consistent with erythema nodosum," appeared on his lower legs. Acetylsalicylic acid therapy was discontinued; the rash lasted less than 48 hours and never reappeared. As the rash was fading, pain in the left sacroiliac joint developed. However, on physical examination, no abnormalities were noted.

During the second week arthralgia of the right temporomandibular joint and the right wrist occurred. During the third week of fever, a repeat complete blood count again showed no abnormalities other than an increased number of bandform PMN's. The ESR was 58 mm per hour. The test for HLA-B27 was positive. Objective evi-

dence of arthritis first became apparent at this time, with tenderness over the right temporomandibular and left sacroiliac joints. Radiographs of these joints gave normal findings. Again, a complete blood count and an analysis of the urine were within normal limits and the ESR increased. Two blood cultures were sterile; a urine culture grew 400 colonies of mixed flora, a stool culture grew normal enteric flora. Antibodies against *Y enterocolitica* were found in titers of 1:320 (type 14 antigen) and 1:160 (type 7 antigen). Agglutinating, hemagglutinating or complement-fixing titers against *Coccidioides,* typhoid O, typhoid H, *Proteus* strains OX2, OXK, and OX19, *Brucella,* influenza A, influenza B, adenovirus, *Mycoplasma pneumoniae,* Q fever, and respiratory syncytial (RS) virus were all within normal ranges.

Fever continued, unless controlled by acetylsalicylic acid, for the next 20 days, with temperatures as high as 39.4°C (103°F). After 17 days persistent pain and swelling of the right elbow, the right ankle and the proximal interphalangeal joint of the right fifth finger developed. Two days later pain, tenderness, limitation of motion in the right shoulder and severe pain with limitation of motion of the left hip occurred. Subsequently, pain in both heels and on the plantar surfaces of his feet when walking, a right knee effusion, and swelling of the left ankle also developed. The boy was severely disabled until treatment with indomethacin was started. There was dramatic improvement within 24 hours with a dosage of 25 mg two times a day. Improvement continued progressively, with gradual recession of joint swelling over the next six weeks, after which he was able to run, play vigorous games and ride his bicycle. However, treatment with indomethacin in dosages as high as 25 mg four times a day was still needed to control polyarthralgia, foot pain and effusion of the right knee four months after onset. Symptoms or signs of urethritis were never present.

CASE 3. A 36-year-old man from Sonoma County, California, was first seen by one of us (S.R.G.) two months following the onset of an illness that began in mid-November 1977. The patient described his condition as a "stomach upset" and diarrhea that lasted three to four days. At about the time that the diarrhea subsided, swelling of the right knee developed, soon followed by swelling of the left knee, left ankle and the left forefoot. Because multiple joint swelling had persisted for three to four weeks without improvement, the patient consulted his own physician who started treatment with phenylbutazone, 100 mg three times a day. A physical examination on January 21, 1978, disclosed swelling and tenderness of the left ankle, particularly over the medial malleolus, together with minimal swelling, tenderness and pain on movement of the second and third metatarsophalangeal joints of the left foot and the metatarsophalangeal joints of both great toes. There was questionable swelling of both knees. A complete blood count and analysis of the urine showed no abnormalities. The ESR was 49 mm per hour; LF and ANA tests were negative. The test for HLA-B27 antigen was positive. Sera for antibodies against *Y enterocolitica* were obtained on July 24 and August 24; they were positive in titers of 1:160 and 1:80 respectively, against the type 7 antigen. X-ray films of the knees, feet and pelvis disclosed no abnormalities. The patient's condition improved slowly through the summer of 1978; when last seen on September 12, 1978, he had only minimal symptoms of pain in the feet, easily controlled with small doses of acetylsalicylic acid. When queried by telephone on January 15, 1979, he reported that he had been entirely asymptomatic for two or three months.

CASE 4. A 35-year-old woman from Santa Clara County, California, noted the onset of pharyngitis, diarrhea, abdominal distension and fever following a visit to Washington state. The diarrhea lasted ten days, with mucus but no blood. Two weeks after the onset of diarrhea, pain and swelling of the left knee, and low back pain in association with fever developed. There was minimal dysuria and difficulty of micturition. The syndrome slowly remitted over the next six months. During the early stages of the illness she lost 20 pounds. She has not had symptoms of eye disease or any other symptoms. Some 24 months following the onset of the illness she has minimal back pain and discomfort in the left knee.

Tests were negative for LF and ANA, but positive for the HLA-B27 antigen. At the onset of the arthritis, the ESR was 58 mm per hour; the hematocrit was 30.8 percent and the results of SMA-12 panel tests were within normal limits. Stool examinations for ova, parasites and other pathogens were negative. Analysis of synovial fluid from the left knee showed a leukocyte count of 9,000 per cu mm, with 48 percent neutrophils and 30 percent lymphocytes. A synovial fluid LF test was negative. No crystals were seen. Serum

TABLE 1.—*Clinical and Laboratory Data for Four Patients With Post-*Yersinia *Arthritis*

Patient	*1*	*2*	*3*	*4*
Age (years)/sex	11/F	13/M	36/M	35/F
Duration of diarrhea (days)	10	4	4	10
Fever	−	+	−	+
Back pain	−	+	−	+
Latent period before onset of arthritis (days)	12	4	4	14
Erythema nodosum	−	+	−	−
Arthritis	+	+	+	+
Conjunctivitis	−	+	−	−
Urethritis	−	−	−	+
Erythrocyte sedimentation rate (mm per hour)	58	56	49	58
Yersinia agglutination titer	1:320	1:320	1:160*	1:80*
HLA-B27 antigen	+	+	+	+
Duration of arthritis (month)	6	4+	12	6

*Specimens submitted for agglutination titers late in the course of the disease.

specimens were obtained four and eight weeks after the onset, and a titer of 1:80 was found for *Y enterocolitica* type 4 antigen on both occasions. Antibody to *Salmonella* was not present.

Discussion

Most of the reports of reactive arthritis following *Yersinia* infection have been from the Scandinavian countries, principally from Finland, where the condition was first described.[1] *Yersinia* infection is known to occur in North America,[6-11] but there have been only a few reports of reactive arthritis following this infection in this continent.[6,8,9] *Y enterocolitica* has recently been reported[12] to be the second most common cause of bacterial gastroenteritis in the Montreal area. No data regarding the incidence of *Yersinia* infection in the United States are known to us. Our experience suggests that *Yersinia* infection may be a more common cause of reactive arthritis or of Reiter syndrome in the United States than hitherto recognized.

Y enterocolitica is difficult to identify as the significant pathogen in stool cultures as they are usually carried out.[11] The growth characteristics and requirements of *Y enterocolitica* have been described by Sonnenwirth.[13] This species of organism grows more slowly at 35° to 37°C than other intestinal pathogens. Stool cultures should be incubated for at least two days before being discarded as negative. Overgrowth of other organisms may occur. Growth and identification of *Y enterocolitica* are greatly dependent on temperature. Identifying tests may be positive at 22° and 25°C, but negative (or delayed) at 37°C. Isolation can be aided by keeping stool specimens at 4°C for one to two days before culture. Thus, *Yersinia* may be overlooked in a stool culture done in a laboratory if a technician is oriented primarily toward detecting *Salmonella, Shigella* or enteropathogenic *Escherichia coli* in cases of infectious diarrhea.

Serologic studies may document infection where stool cultures have not. In a careful study of 60 patients seen over two years in Finland, Leino and Kalliomaki[14] depended largely on elevated antibody titers to establish the diagnosis in patients who presented with findings of fever, diarrhea, abdominal pain, erythema nodosum and arthritis to suggest yersiniosis. In their patients, the lowest significant titer was 1:160. Ahvonen,[15] in a serologic study of 334 cases that fulfilled clinical and laboratory criteria for the diagnosis of *Yersinia* infection, reported that the titer usually attained its maximum value after one or two weeks of illness, and then gradually declined. A significant drop in titer had usually occurred within two months, but was sometimes delayed. Ahvonen also carried out a study involving 1,580 Finnish blood donors, finding only 4 (0.25 percent) persons with *Yersinia* titers of 1:160 or greater. In this study, there were 56 persons (3.5 percent) with titers of 1:40 or 1:80. We know of no similar studies having been done in the United States.

Paired antibody determinations should be done to establish clearly that *Yersinia* organisms are the significant infectious agent in cases where it is not possible to recover organisms by stool culture. The first specimen should be drawn as early as possible in the course of the illness, and the second four to six weeks later. A titer of 1:160 or greater in at least one of these will suffice to support a diagnosis of *Yersinia* infection. Usually, the highest titer can be expected in the first specimen, with a fall of one tube dilution or greater in the second. Because we failed to obtain paired specimens in cases 1 and 2, and obtained paired serologic studies late in cases 3 and 4, the condition of the patients we report here can most accurately be identified as "possible post-*Yersinia* arthritis." In case 4, where the titers, in specimens obtained four and eight weeks after onset, were both 1:80, the minimum criterion of a 1:160 titer was not observed. We report this case because illness of the sort that occurred, in a patient with the HLA-B27 phenotype, should strongly

suggest either yersiniosis or post-*Salmonella* or post-*Shigella* arthritis. Failure to show a significant titer at four and eight weeks after onset underscores the importance of obtaining the first serologic specimen early in the course of illness. (Serologic studies reported here were carried out by the Microbial Diseases Laboratory of the State of California, Department of Health, 2151 Berkeley Way, Berkeley, CA 94704.)

Table 1 presents similarities and differences in clinical and laboratory data for the four cases reported here.

Conclusion

The four cases reported show that reactive arthritis following enteritis due to *Y enterocolitica* may occur in persons residing in Northern California, a syndrome previously reported most frequently in Scandinavia. Because reactive arthritis is known to occur with greatest frequency in persons who are HLA-B27 positive, a test for this antigen should be done in patients in whom arthritis in association with a febrile or diarrheal disease has developed, particularly if *Yersinia*, *Salmonella* or *Shigella* infection is suspected or proved. At this time the prognosis for these patients is not known. It had been thought that this syndrome was always self-limited, but Calin and Fries[3] have found some patients with prolonged and persistent arthritis following diarrheal disease due to *Shigella*.

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Death Following Inhalation of Mercury Vapor at Home

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THE INHALATION of toxic fumes and metallic vapors is a fairly common occurrence in industry. There are ample accounts describing the effects from the inhalation of vaporized mercury on the respiratory tract and other organ systems.[1-5] Ramazzini[6] in 1940 gave one of the earliest descriptions of the consequences of such exposure. Studies indicate that members of the dental profession and workers in the fur or felt hat-making industry have been at greatest risk for exposure to mercury.[2] Other industrial exposures have occurred primarily when metallic mercury has been accidentally vaporized in a high-temperature environment.[3-5]

Fortunately, deaths among adults exposed in industry have been very rare.[4] In contrast, accidental exposure to mercury has resulted in deaths among children and has caused chronic disability in adults. In the following report we discuss what appears to be the first death of an adult exposed to mercury vapor in the home. We have included hemodynamic measurements, which have not been described previously in these patients.

Report of a Case

A 53-year-old man, suffering from severe respiratory distress, was transferred to the Los Angeles County/University of Southern California Medical Center for specialized renal and respiratory care. He had been in good health until approximately two weeks before admission. At that time, while the patient was working with elemental mercury in an ore distillation process on his kitchen stove, chills, fever, dyspnea, headache,

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ABBREVIATIONS USED IN TEXT

CPAP = continuous positive airway pressure
ECMO = extracorporeal membrane oxygenator
PEEP = positive end-expiratory pressure

red spots in front of his eyes, diarrhea and abdominal cramps developed. A few hours later he complained of partial blindness; however, all the symptoms gradually disappeared over the next two days. Six days before admission he again heated some ore and mercury mixture over his kitchen stove for about 20 minutes. Shortly thereafter he noted the room becoming dark, and the red spots in his eyes reappeared. He became weak, vomited once and then experienced headache, chills, fever and diarrhea. These symptoms continued for the next four days. He then became rapidly and increasingly short of breath, and was admitted to hospital the next day. At that time he was found to be cyanotic, in acute respiratory distress, and having severe abdominal cramps. A roentgenogram of the chest showed bilateral lung infiltrates consistent with pulmonary edema. Because he had had a myocardial infarction within the past year, a balloon-tipped floating catheter was inserted into the pulmonary artery. The pulmonary artery and wedge pressures were reported to be normal. A tracheostomy was done and his respirations were mechanically assisted. The level of mercury in his urine was 5 mg per dl. Because charcoal hemodialysis was being considered he was transferred to the medical center. On arrival, the patient's temperature was 37.1°C (98.8°F); blood pressure, 130/100 mm of mercury; respirations, 18 per minute when assisted by a ventilator, and pulse, 76 beats per minute. He was alert, oriented and in no apparent distress. At this time, he was not cyanotic. Inspiratory rales were present in both lung bases. There were hypoactive bowel sounds. Results of the neurological examination showed no abnormalities. The initial pulmonary artery pressure was 34/20 mm of mercury, with a mean wedge pressure of 10 mm of mercury. A roentgenogram of the chest (Figure 1) showed extensive bilateral pulmonary infiltrates but no evidence of cardiomegaly. An analysis of arterial blood gases, while the patient breathed 70 percent oxygen, with a positive end-expiratory pressure (PEEP) of 12 cm of water, showed oxygen pressure (Po_2) 73 torr; pH 7.42; carbon

Figure 1.—A roentgenogram of the patient's chest showing extensive bilateral pulmonary infiltrates but no evidence of cardiomegaly.

dioxide pressure (Pco_2) 35 torr, and bicarbonate 22 mEq per liter. Other laboratory data were as follows: hematocrit 48 percent; hemoglobin 16.6 grams per dl; leukocyte count 20,000 per cu mm, with 89 percent polymorphonuclear cells, 5 percent bands, 5 percent lymphocytes and 1 percent monocytes; occasional erythrocytes contained inclusion bodies resembling siderocytes. An analysis of the urine showed a specific gravity of 1.025 and pH of 5.5; proteinuria (1+); glucosuria (1+); and one to two pus cells, zero to one erythrocyte, no casts and few bacteria per low-power field. Blood chemistry measurements were within normal limits except for the following: sodium 131 and chloride 94 mEq per liter; and glucose 172, urea nitrogen 45, uric acid 9.6 and creatinine 1.5 mg per dl. Lactic dehydrogenase measured 2,400 units. The urinary concentration of mercury was 3,700 μg per liter (normal, up to 20 μg per liter). Other urine measurements were sodium 40 and potassium 54 mEq per liter; osmolality 792 mOsm per liter, and creatinine 102 mg per kg of body weight per 24 hours. Findings on an electrocardiogram showed an old inferior myocardial infarction.

Following intravenous administration of 500 ml of 5 percent dextrose in water over four hours the patient's pulmonary artery pressure rose to 40/24 mm of mercury, with the mean wedge also rising to 22 mm of mercury. His urinary output was 100 ml per hour. The intravenous infusion rate was lowered, resulting in a lowering of the wedge pressure. During the next four hours his respiratory support was converted to continu-

ous positive airway pressure (CPAP) with a fraction of inspired oxygen (FIO_2) of 0.5. He was given a course of dimercaprol (BAL in Oil). By the seventh hospital day the urine mercury level was 660 μg per liter. The urea nitrogen and creatinine levels fell to within normal range and he continued to excrete adequate urine. With continued modest fluid restriction his serum sodium and chloride concentrations returned toward normal. On the ninth day he suddenly complained of pain in the right side of his chest, and acute tachypnea and respiratory distress developed. A roentgenogram of the chest showed a massive pneumothorax and empyema. Chest tube drainage was instituted. *Pseudomonas aeruginosa* and coagulase-positive *Staphylococcus aureus* were isolated from the tracheal aspirate. He was given tobramycin and methicillin. Because it became increasingly difficult to maintain adequate oxygenation with mechanical ventilation, the patient was transferred to another facility for extracorporeal membrane oxygenator (ECMO) support. During the next 24 hours, before ECMO could be carried out, there seemed to be improvement, which continued for the next 12 days without ECMO. However, the pneumothorax with bronchopleural fistula persisted, and tracheomalacia developed as well. The patient's condition then worsened: he acquired nosocomial pneumonia and died during the third week of this hospital stay.

Discussion

This patient undoubtedly died from nosocomial pneumonia, but, unquestionably, a strong contributing factor was his two brief but severe exposures to mercury vapor. His symptoms and signs during both episodes were similar to those which have been previously reported. The delayed onset of respiratory distress that followed the initial symptoms is also characteristic. The classic description by Matthes[7] of the symptoms experienced by a mother and her three children exposed overnight to fumes emanating from a gas stove, which had been freshly painted with paint that contained mercury, has been repeated in other accounts of accidental exposure. Hallee[8] reported a family of five who were exposed to mercury vapors when the father used the metal to extract gold from gold sand over a kitchen stove. Their presenting symptoms and signs matched those seen in our patient. His exposure history was virtually identical except that the dose was probably higher because his exposure occurred on two occasions over a short time.

Although the dose of exposure is best determined by measuring the concentration of mercury in whole blood,[9] most accounts of inhalation injury report concentrations of the substance in urine. Because urine levels are both protracted and irregular,[10] it does not accurately reflect the high levels achieved soon after exposure. When one considers that normal levels of mercury in the urine are 0 to 20 μg per liter, then our patient's levels were certainly in the high toxic range. Urine levels in patients with similar symptoms and pulmonary alterations have been reported to be between 540 μg and 2,100 μg per liter per 24 hours.[11]

Although the dose of mercury usually inhaled by most persons is not lethal, deaths have occurred. Campbell[12] reported the first known death, that of a 4-month-old infant who had been exposed to a teaspoon of mercury vaporized over a hot kitchen stove. At autopsy, the child had pulmonary edema, renal tubular damage and mucosal necrosis of the stomach and duodenum. These organ systems as well as the brain are considered to be major sites of deposition of mercury after it is absorbed through the lungs and into the blood. In the detailed postmortem examination of the three children in the report by Matthes,[7] there was erosive bronchitis and bronchiolitis, with severe interstitial pneumonitis and hyaline membrane. There was also alternating alveolar collapse or emphysema and pneumothorax. Only minor changes were seen in the liver and kidney. During the early course of our patient's illness a pneumothorax developed. Although possible, the mechanical support of his breathing (CPAP, 8 to 10 cm of water) probably was less at fault than were the morphological changes caused by his underlying illness, which made the lung more susceptible to barotrauma.

The radiological appearance of the lungs in our patient is consistent with that described previously.[4,8,13] These all reflect the development of acute noncardiogenic pulmonary edema. The pulmonary artery pressure measurements support this diagnosis in our patient. Even though he had a history of previous heart disease, the mean wedge pressures were persistently normal during the early hours of his acute illness. Later, his wedge pressure rose after fluid administration, which may then have reflected some myocardial malfunction.

Teng[14] described the radiological abnormalities seen in the children reported by Matthes[7] and correlated them with changes seen at autopsy. There were substantially depressed diaphragms, ill-defined areas of increased radiodensity due to pulmonary edema, diffuse alveolar and interstitial emphysema, and pneumothorax.

The distribution of inhaled mercury vapor has been extensively studied. Berlin[15] compared the concentration of mercury deposited in the brain of mice given equivalent doses of either the inhaled vapor or mercuric nitrate by intravenous injection. Uptake was ten times greater by the former route. Kudzk[16] allowed four human subjects to inhale mercury vapor and measured the inspired and expired concentrations. From his results he concluded that the absorption of mercury was almost complete and was independent of the dose inhaled. Teisinger[10] exposed a group of volunteers to 100 mg per cu mm of mercury vapor for seven hours. About 76 percent of the mercury was retained in the mouth and nose. Therefore, the actual amount absorbed could not be accurately estimated. On the other hand, Berlin and co-workers[17] reported that when guinea pigs inhaled mercury vapor the highest concentrations of the substance were found in the periphery of the lung, and that most of the mercury was quickly transferred to the blood. Only a small fraction remained in the lung tissue, and this was slowly distributed to the rest of the body. Using radioisotope techniques, Hayes[18] found similar results in rats. Matthes[7] measured mercury concentrations in tissue from the livers, lungs and kidneys of the children who had died. The highest concentrations were found in the kidneys (60 to 79.1 mg per kg of body weight) whereas the lungs had the lowest amounts (6.3 to 9.3 mg per kg of body weight). One must conclude that the inhalation of mercury vapor, even in small concentrations, exposes a person to a very highly toxic substance, which can lead to serious or lethal complications.

Had our patient survived, one could speculate on the long-term outcome of his exposure. There are only two accounts which deal with the late effects on persons who have inhaled mercury vapor. In the first report, Hallee[8] noted that the father (who had received the most serious exposure and who had persistent abnormal pulmonary function) had evidence of diffuse alveolar fibrosis on a lung biopsy done five months after exposure. He and his family had been exposed to no more than 30 ml of mercury vapor. The second account[4] describes six workers who were exposed to mercury vapor from a broken thermostat for approximately eight hours. All were symptomatic, and roentgenograms of the chest showed abnormalities in three. They all complained of persistent impotency, fatigue, and vague personality disturbances that continued for as long as eight years after the accident.

Treatment for this problem, beyond symptomatic support, is disappointing. Immediate support with CPAP or, if the victim is hypercapneic, with mechanical ventilation with PEEP is appropriate and indicated. Our patient initially responded to this form of therapy. The only therapy suggested to promote the elimination of mercury from the body is dimercaprol. However, it has not been shown to be highly successful. The recommended dosage is 3 mg per kg of body weight every six hours for three to four days.[11] Charcoal perfusion hemodialysis, although initially considered by us, may be inappropriate and probably is not an efficient method of eliminating mercury bound to the tissues. Finally, all efforts should be made to prevent the development of a nosocomial lung infection, which, unfortunately, occurred in our patient.

Clearly, the best way to prevent such a mishap is to avoid exposure. However, even the most well-intentioned, but unknowledgeable, persons can become exposed to the hazards of mercury vapors.[13,19] It then becomes essential for physicians to understand the urgency for taking optimal therapeutic measures so that the survival of such patients may be assured.

Summary

On two separate occasions, a 53-year-old man inhaled mercury vapor while heating the metal over a kitchen stove. Noncardiogenic pulmonary edema developed (diagnosis supported by hemodynamic measurements) from which he temporarily recovered. However, he died subsequently from nosocomial pneumonia. This may be the first recorded death of an adult in a nonindustrial setting.

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Testifying in a Hearing Loss Case

WHEN I HAVE TESTIFIED as to the noise exposure [in a hearing loss case] . . . it has always been discounted when I have taken a history or the nurse has taken it, either because it is not accurate or the patient can say he did not understand it and it was not recorded right. So now I have three forms: one is a history of occupational noise exposure, the second one is about nonoccupational noise exposure, and the third is about military noise exposure. The individual patient fills these out himself as to the time he was employed with a certain company, the type of exposure, whether he wore ear protection or not, what he thought about his hearing and whether he had any hearing tests done during that time. . . . These stand up in court, and get you out of the position of misinterpreting what the patient said.

* * * * *

IN MY DEPOSITION, I usually make a statement along these lines: "Given this patient's history, certain facts appear evident, and this is valid if the patient is telling me the truth." Then it is up to the judges and the lawyers to determine whether the patient is telling you the truth or not.

—MANSFIELD F. W. SMITH, MD, *San Jose, California*
—MICHAEL E. GLASSCOCK, III, MD, *Nashville, Tennessee*

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Orthodox Medicine Humanistic Medicine Holistic Health Care

IN THE DECEMBER 1979 issue the editors began a forum for discussing orthodox medicine, humanistic medicine and holistic health care. The response from readers has been so great that contributions to the forum no longer can be accepted. A future issue of the journal will carry a summary of the dialogue and discussion.

—MSMW

Holism Since Hippocrates

ALEX WEISSKOPF, MD

THE INTRODUCTION to the special forum in the December 1979 issue of the WESTERN JOURNAL invites discussion of the articles on holistic medicine.

Santayana is quoted as having said "Those who cannot remember the past are condemned to repeat it." Thus, again, we see the wheel being reinvented. I entered these articles with relish hoping to become informed of the *new wave* in healing. Sadly, I found nothing that has not been a part of the teachings of *orthodox* medicine since prehistoric times. It does not hurt the practicing physician to be reminded of the truisms of the whole person but this is not holism, but the fundamentals of our teachings. We physicians were weaned on the concepts of humanity, love, kindness and sensitivity. Hippocrates, Maimonides, Osler and Ingelfinger, all of whom were quoted by these Holists, were orthodox physicians.

It is gratuitous for authors who are not actually taking care of patients to state "For healing . . . is as much related to one's capacity to give and to receive love as it is to the ministrations of the physician."[1] These articles infer, if not state, that physicians are great mechanics who tinker with pieces of human beings, but that in Holistic medicine we find the solution as a "relatively recent [sic] manifestation consistent with this fundamental quest [for optimum health] of all humankind."[2]

Holism is as recent as Hippocrates and Maimonides and as original a concept as "the whole is greater than the sum of its parts," a philosophic consideration since Greek days and the basis for the 19th century Gestalt psychology.

These articles defy reason by assuming that there are areas of the environment and human behavior that are too broad and complex for the "already busy physician" and that "other health professionals should be specially trained to deal with them."[3]

I do hope that some future articles will clarify Holism and place it in proper context within *orthodox* medicine. The concepts of Holism are not new and, though we may not emphasize them enough, they have been part and parcel of medical practice since the first shaman beat his drum.

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Refer to: Weisskopf A: Holism since Hippocrates, *In* Orthodox medicine, humanistic medicine and holistic health care—A forum. West J Med 132:544, Jun 1980

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Orthodox Institutions and New Theories

DANA ULLMAN, MPH

WILLIAM JAMES described the way orthodox institutions react to new theories. He said there are three stages to their development and acceptance. First, they are attacked as absurd. Then, they are admitted to be true but are thought to be obvious and insignificant. Third, they are seen to be so important that the orthodox institutions claim they discovered them.

Until very recently, holistic health was thought to be sheer quackery. Physicians scolded their patients for even thinking of trying these practices. The few physicians who began experimenting

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with holistic approaches to health were ridiculed by their peers for utilizing unproven methods. Now, as shown by some of the articles in the present forum, many physicians are beginning to recognize that holistic health concepts and practices are valuable to health care; however, they assume that these concepts and practices are so obvious that orthodox medicine today has taken what is needed from them and left behind what does not work. Further, the forum articles have assumed that physicians have been practicing holistic health for a long time and that they should maintain control over its practice.

Dwight L. Wilbur ("A Balance of Science and Art," January 1980) said orthodox medicine "has always encompassed the whole person—the psyche as well as the soma and the interrelationships of physical, emotional and psychic factors in health and disease." John R. Green ("A Pluralistic Approach," January 1980) affirmed that a pluralistic approach is needed in health care; however, he also said "all of medicine is one and physicians should play the leading role in its application."

It is difficult to believe that physicians have *only* taken what is valuable from the past and that physicians have long practiced holistically. Medical history is replete with examples of valuable knowledge and practices that were buried and left unused because the orthodox institutions at the time did not understand their true significance. As for our present time, it seems highly unlikely that physicians can offer whole person health care when statistics show that most doctor visits average less than ten minutes.

I am particularly concerned that some physicians are now trying to assume control over a field of practice in which they were not trained. Although one can predict this action from William James's insights, I feel it is now important to recognize how holistic health care both complements *and* is different from orthodox medicine.

One of the most obvious differences at present between holistic health and orthodox medicine is that many holistic health practices assume that a "life energy" (described as "chi" in acupuncture, "bioenergy" in psychic healing, "vital force" in homeopathic medicine, "prana" in yogic practices, to name a few) functions within and animates the human organism, while orthodox medicine assumes the human organism functions only as a physiochemical system. These holistic health perspectives seek to promote or maintain health by stimulating, nourishing or balancing this underlying life energy. Orthodox medicine, in comparison, generally attempts to cure or prevent disease by affecting the physiochemical process of a localized disease. Although the life energy concept is foreign to most practitioners of orthodox medicine, the historical and transcultural application of it in healing,[1,2] as well as the present infant stage of research into subatomic energies and fields of life,[3-5] begins to provide the empirical basis for understanding and utilizing this mystical law of nature.

When these two approaches are each understood and respected, there is greater potential for their complementary function. The lack of understanding and respect for each approach, however, may lead to a philosophical and therapeutic conflict that fails to utilize the optimal features of each practice and diminishes their complementary potential.

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Holistic Hype

WILLIAM R. PHILLIPS, MD, MPH

MEDICINE IS THE professional discipline of helping people improve their health. Modern physicians draw upon a full spectrum of resources, from ancient art to the frontiers of science, in a constantly evolving effort to help people toward that goal. There is no orthodoxy in medicine. Physicians' professional commitment to their patients requires only that the interventions they suggest are proved to be superior to the available alternatives and to have value that outweighs the associated risks.

Cultists restrict their prescriptions on the basis

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of belief. Faddists follow fashions or create their own. Entrepreneurs slant their offerings to contemporary markets. There is no room in the helping professions for competition between practitioners defensively extolling their personal methods or aggressively criticizing those of others. Our aim is to help people help themselves, and only an open-minded eclectic approach puts the needs of patients above our own. Holistic health, high-level wellness and the proliferating assortment of health practitioners seeking identity in these alternative ideologies seem out of place as they vie for followers, finances and fame. That which is proved from their experience and experiment demands to be integrated into regular medical practice. The rest, if its value cannot be objectively substantiated, deserves to be excluded from the practice of professionals.

The secret of caring for a patient has always been to care for the patient. Today the secret is also to care enough to seek constantly to answer two questions: Am I offering everything that can help? Does everything I offer help?

A Visit from the Healer

ROGER KEENEY HOWE, MD

ONE DAY the great healer Malesh came to the town of Bethel. The people came to him, some to be healed, others to observe him at work, some to question him and learn from him. It was known to all the people in these parts that Malesh was a great teacher; he was fond of saying that his knowledge was of no use unless shared.

One man came to him with a complaint of a stomach ache. Malesh spoke quietly with him for a few moments, then said to him "You must trust in God. He will provide for you, and He shall relieve your pain." Malesh placed his hand on the man's abdomen, and together they shouted "Hallelujiah! Hallelujiah!" The man smiled, said he felt much better, and left.

A woman came to him with the complaint of a backache. After a few questions and a brief examination, Malesh caused her to lie on a padded table. For a few moments he massaged her back, then he bent her. There was a loud "pop," then another. The woman smiled, thanked Malesh and departed.

One of those who came to observe and question Malesh said "I observe that you are a man of God, and heal by faith. This is certainly good. I also have a strong faith. It fills me with awe that the power of the Lord thus flows through you to produce a cure. In spite of my faith, however, I have failed. I am cut and would be healed. Will you help me?"

He showed Malesh a cut on his arm which was long and deep, but clean. Malesh washed it with clean water and soap, put a plaster of ground root onto it and bound it with clean bandages. He said "Some things the Lord has made your body to do for you without his assistance. This is one. He gives us the root and our hands with which to heal such things. Keep the bandage clean and dry; in seven days you shall be healed."

The man looked puzzled by this, but thanked Malesh and sat back down in the circle to observe and learn more. Another man rose and limped to where Malesh stood. "Malesh, healer, you are a user of the natural healing methods, much as I am. I have known of the ground root which you used on this other man, but it has not healed my wound. What herb would you use for this?" The man rolled up his pant leg and showed a large, red, raised area with pus draining from it down his leg. Malesh looked upon it and spoke thus: "My friend, herbs have limits to their effectiveness. They will not heal all things. Man himself makes some stronger medicines which suffice where nature's remedies fail. I give you these tablets to take one with each meal and one at bedtime until they are gone. This is a powerful medicine which will travel through your bloodstream to fight this infection. You will find yourself healed in ten days."

This man also looked puzzled, but thanked Malesh and resumed his place. A woman who had been sitting quietly now led forward her father. He was an old man who was bent forward and breathed with difficulty.

"Malesh," said the woman, "you are very wise and know all the answers to our problems. Please will you heal my poor father who cannot breathe?"

Malesh began to examine the old man, listening to his breathing and making tests on his lungs. As he did so, he answered the woman: "You are

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mistaken to think I have all the answers. To no one person is it given to know *all* the answers. Anyone who thinks he or she knows them has yet to ask the important questions. I have come to know that I don't even know all the questions —each new answer I learn leads me to many new questions I could never have known before. To think you know all the answers or all the questions is a self-delusion born of a closed mind. It is better to keep the mind open to all questions, all information, for there is no one so simple that he or she cannot teach us something."

He finished his examination of the old man, and told him and his daughter that the old man had a lung disease which was not susceptible to cure with Malesh's present knowledge, but which would be made more tolerable by life in a clear atmosphere nearer sea level. The two departed.

Another man came forward, telling of a pain in his right side. Malesh examined him briefly and inserted three long needles into the man's left ear. The man smiled. Malesh bade him wait for a few minutes.

An old woman came forward with a large lump in front of her left ear. She requested Malesh to cure it. He spoke briefly with her, then washed the lump and used a syringe and needle to inject a clear fluid beneath it. He washed his hands carefully, then took several tools from his kit. He made a cut around the lump with a knife and removed the lump, then used a needle and thread to close the cut. As he did this, the man whose arm he had bandaged said to him "But Malesh, you do not maintain the purity of your healing. You must not cut, but should use the divine powers you possess to heal by faith."

"My friend," answered Malesh as he worked, "you fail to see the importance of what I have told the lady a few moments ago. Just as no man may have all the answers, so may no single philosophy of healing answer all of man's needs. The need of my art is not to maintain its philosophic purity, but to heal the sickness of the body, to promote the health of both the body and the mind. If one philosophical school teaches me better than another to cope with the problem at hand, should I not use that knowledge? If my mind is open and my healer's heart pure, how can I bypass an effective remedy, regardless whence it came or who spoke it?"

"But," rejoined the man, "our church teaches that the only path to salvation is by faith in our Lord and Savior. Our church teaches that it is the very pathway which is of importance, that to lack in faith is the ultimate sin."

To this Malesh answered "Are not the religious leaders trying to elevate the soul of man? Can any among them claim *all* the answers, to know *all* the mysteries and secrets of the universe? Only if they close their minds to the truth before them! To elevate the soul may require quite different things for different people with different problems at different places and times. For some, the impediment may be an unsound body or mind, in others the problem is how to purify the soul. Any technique that helps the soul approach perfection is valid, regardless whether it fits any one philosophical construct."

Malesh turned, and with one of his surgical tools pointed to the nearby mountain. "When you wish to climb to the top of the mountain, is it not reaching the top which is the goal? One route may be easier and another harder, but are not all routes which lead to the top valid? To dwell too much on the pathway is to lose sight of the goal. Your faith did not heal your arm, but the naturopath's herbs shall do so—would you rather have the cut or the healing? The naturopath's art would not heal his leg, so he is taking the physician's medication to accomplish the purification his art could not do. Is it not the healing which is important?"

The lady's cut was by this time repaired, and she listened to Malesh before leaving him. Malesh removed the needles from the man's ear; he thanked Malesh for the relief of his pain, and walked away.

At this point a small child was carried to Malesh by her father. "She is ill, Malesh. Last night she could keep no food in her stomach. Today she has no hunger, and her belly hurts her. Please help her."

Malesh showed the man to lay her on the padded table. His hands rested on her briefly. He moved her legs a little, then said "Your daughter is seriously ill. It is important that we take her to the hospital and operate soon. Please come with me." Leading the father, who was again carrying his little daughter, Malesh left.

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Adult Kawasaki Disease—Three Occurrences in the Same Patient

To the Editor: Medical journals are reporting similar syndromes which have been called "adult Kawasaki disease" or "staphylococcal toxic-shock syndrome."[1,2] Infectious disease experts throughout the country are obviously highly interested in the description of a possible new disease entity. I understand there are only one or two cases in which the illness has recurred once and wish to report a case in which, I feel, the illness occurred three times in the same patient.

Report of a Case.

A 16-year-old woman was first seen July 8, 1977, with complaints of fever, abdominal pain, nausea and severe headache. She had just started her menstrual period and there was no diarrhea. On physical examination the woman appeared very ill and the following findings were noted: tachycardia of 130, temperature 40°C (104°F), a reddened throat, with moderate cervical adenopathy, tenderness in the right upper quadrant of the abdomen, and a fine maculopapular erythematous rash on the face, chest and extremities. Cultures of the blood, throat, urine and spinal fluid were negative. Leukocyte count and serum glutamic oxaloacetic transaminase were elevated, as were the alkaline phosphatase and serum glutamic pyruvic transaminase. The patient appeared to be going into shock, with a blood pressure of 80/44 mm of mercury within eight hours of admission. Myalgias remained prominent during the first 72 hours. Mononucleosis spot and hepatitis associated antigen (HAA) tests were negative. Results of nuclear binding antibody and rheumatoid titer studies were within normal limits. Following treatment with ampicillin and kanamycin, the patient was discharged on the fifth hospital day after being afebrile 24 hours. Within two weeks, results of all liver function tests were normal.

One month later, on August 11, the patient returned with similar symptoms of fever, headache, myalgia, and chest and abdominal pain; vomiting had occurred but not diarrhea. One day after the onset of symptoms her menstrual period started. Her lowest blood pressure measured 74/34 mm of mercury, and right upper quadrant tenderness again was noted. The initial leukocyte count and serum amylase value were elevated. All cultures were negative except that *Staphylococcus aureus,* coagulase-positive, greater than 10^5 per cu mm, was cultured from the urine. X-ray and ultrasound studies of the gallbladder as well as an intravenous pyelogram, showed no abnormalities. This time the patient was treated with chloramphenicol and became afebrile three days after admission. Two weeks later all laboratory data were within normal limits including urine culture.

The third and most serious episode occurred two years later, in September 1979, when the patient was admitted on the third day of her menstrual period with complaint of hip pains, fever and general myalgia. On examination the patient again appeared ill, with a flushed face, fever, tachycardia, red throat and some upper abdominal tenderness. Puffiness of the face, wrist and hands was quite noticeable. Initial leukocyte count equalled 10,400 but rose to 15,600 within a few hours. All cultures were initially negative, and HAA antigen, nuclear binding antibody and febrile agglutinin studies showed no abnormalities. Antistreptolysin-O (ASO) titers were 166 Todd units on two occasions. The patient again appeared to be going into shock, this time having a decreased urinary output 24 hours after admission with rising blood urea nitrogen and creatinine values. A second urine culture grew *Staphylococcus aureus* from a catheterized specimen. During this hospital stay liver function tests were normal. For the first time the erythrocyte sedimentation rate became elevated, rising from 4 to 52 mm per hour during her hospital stay of eight days. The muscle pain was more severe, and the

rash more extensive with this third bout. Peeling of the fingers and palms of the hands was noted and had also occurred following her hospital admissions two years before.

Her illnesses resemble the staphylococcal toxic-shock syndrome described by Todd,[3] and further discussed in the *Utah State Communicable Disease Newsletter*.[4] Awareness of this syndrome (which does not appear to be rare), and further reporting by clinicians will aid those investigating its cause and management.

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Holistic Advice for Life-Threatening Conditions

To the Editor: Dr. Robert Raskind is to be commended for his straightforward statement of skepticism [Holistic Medicine for Neurosurgeons] in the March 1980 issue of the journal. His is a valid criticism of those proponents of holistic medicine who tell him that he " '. . . should not treat the tumor, but should treat the patient' " without telling him what he might say or do for the patient and how this fits with his role as physician.

It is not reasonable to expect those not having an intuitive appreciation of this approach to medical care to begin to understand it through philosophical discussions about treating the patient and not the disease. Most physicians evolved their sense of their roles and responsibilities vis-a-vis their patients through the repetitive experience of the clinical encounter, beginning as medical students with the observation of their teachers (the most highly esteemed of whom were generally researchers in the esoterica of subspecialties, and showed it), and progressing through the often tedious experiences of the years of residency. Any change in this sense will be achieved only through the same avenue—the specific clinical situation.

Unfortunately, Dr. Raskind could only give a very general description of the case he provided as an example. Nevertheless, I will risk some concrete observations. First, I would suggest that there are several antecedent questions that Dr. Raskind would do well to ask to help determine what his role in the patient's care might be: (1) What is the likely course of this patient's disease after craniotomy and excision of the lesion, and how does that compare with what it would be without a surgical operation? (2) How does the patient feel about the different outcomes presented by these alternatives? Indeed, unless the patient has indicated a wish for his life to be preserved whatever this may cost in residual impairment, simply asking how to go about preserving the patient's life, Dr. Raskind's first question, is irrelevant.

In this respect I would fault Dr. Raskind's critics for strongly (and blindly) advising against a surgical procedure, as much as I might fault him for the opposite. The essence of holistic medicine is a regard for the uniqueness of the patient's life, and to the extent that we cannot stand in another's place, we must be cautious about the advice we give. Where the risk of the disease is significant and the risk of the treatment insignificant (for example, in the use of diuretics for hypertension) this obviously is of minor consequence. But where the disease is life-threatening regardless of treatment and the available treatment carries its own set of complications, as is the case here, then due respect for the patient requires that when we go beyond presenting alternatives for the patient's choice (to answer the almost invariably asked question, "What do you advise I do, Doctor?"), we make clear that we are stepping out of our positions as experts and are answering on the purely personal basis of what we would do were we to find ourselves in a similar situation.

One guideline for the management of these life-threatening conditions, which Dr. Raskind requested and which he might find useful, is that a well-informed patient is the person best equipped to make the critical decisions affecting his or her life, and the physician is in the best position to assure that the patient is well informed about the relevant issues regarding the illness and its treatment.

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Special Article

Refer to: Myers BA, Leighton R: Medicaid and the mainstream: Reassessment in the context of the taxpayer revolt. West J Med 132:550-561, Jun 1980

Medicaid and the Mainstream: Reassessment in the Context of the Taxpayer Revolt

BEVERLEE A. MYERS, MPH, *and* RIGBY LEIGHTON, MS, *Sacramento, California*

California's Medicaid program—Medi-Cal—attempted to implement the ideal of mainstream medical care for the poor by giving program beneficiaries a "credit card" for use in the private health care marketplace. This exposed the program to the perverse economic incentives of the fee-for-service, cost-plus health care system, and contributed to a high rate of increase in program costs. Attempts to control costs have been equally perverse, resulting in low payment rates, the second-guessing of physician professional judgments, the probing of medical and fiscal records, and the use of computerized surveillance systems.

Attempts to shift to the use of more efficient delivery systems have had small success. Attempts to attain cost containment through restructuring the Medi-Cal program have been rejected in the name of the mainstream ideal. Costs have continued to escalate, with annual increases as high as 20 percent in some years. Medi-Cal now costs $4 billion per year, the largest single program in California state government.

The taxpayer revolt in California is creating a fiscal crisis that will force rethinking of the premises of publicly funded health care for the poor, and a restructuring of strategies for reaching that objective. In the short run, it appears that the issue may not be whether the indigent will have access to mainstream medical care, but whether they will have access to any *medical care. In the longer run, the crisis should represent an opportunity for building a system of health care that can serve the financially disadvantaged at a cost tolerable to our society.*

"We can no longer afford a private, fee-for-service system of health care dependent solely on the good will of private providers."

WESTERN CENTER ON LAW AND POVERTY LETTER TO GOVERNOR EDMUND G. BROWN JR.
December 12, 1978

Ms. Myers is Director of the California Department of Health Services and Mr. Leighton is policy consultant of the California Department of Health Services.

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The Original Vision

THE FEDERAL PROGRAM of grants to states for medical assistance to the poor and disabled—now universally known as Medicaid—was brought into existence by the Social Security Amendments of 1965 (Public Law 89-97), along with the federally administered Medicare program. It represented a significant victory for those who be-

lieved that no person should be deprived access to necessary health care because of inability to pay. California was one of the first states to take advantage of the new federal grants; enabling legislation was passed in 1965 and the Medi-Cal program was implemented in March 1966.

The tenor of those times is captured well in this excerpt from a recently published interview with Paul Ward, currently President of the California Hospital Association, who in 1965 was Secretary of Health and Welfare in California:

> Momentum developed in California for mainstream medical care, for the idea that everyone was entitled to high quality care. We even went so far as to say that the poor should have a credit card, much like the middle class. When they needed medical care, they would simply go to the hospital and show the card, get the care and go on about their way. We were ridiculed tremendously for that idea. So we drew back.[1]

Although there may have been a drawing back from the credit card approach in its pure form, it remained an essential principle of Medi-Cal (and Medicaid programs generally) that the objective was to permit the poor to buy into the mainstream of the health care system. Following is a key part of the Medi-Cal enabling legislation:

> It is intended that whenever possible and feasible: (a) The means employed shall be such as to allow, to the extent practicable, eligible persons to secure health care in the same manner employed by the public generally, and without discrimination or segregation based purely on their economic disability.[2]

Although conditioned by the phrases "whenever possible and feasible" and "to the extent practicable," the intent of mainstreaming is still clearly expressed in the phrase ". . . the same manner employed by the public generally."

The Price of the Vision

Thus, the basic operational principle for Medi-Cal was to give the program beneficiary a form of purchasing power in the private health care marketplace. The Medi-Cal identification card did become a type of credit card, although it soon became evident that controls would be needed in order to avoid bankruptcy of the program. Tables 1 and 2 illustrate the Medi-Cal cost issue in its simplest manifestation—the growth in number of eligibles covered by the program and the growth in the dollars expended.

According to Paul Ward, this growth rate was to be expected:

> Nothing new is developing in the Medi-Cal program that wasn't predicted. If you go back to the original testimony given on the Medi-Cal program, Mark Berke who was then President of the California Hospital Association, predicted that the cost of medical care would reach 10 percent of the gross national product, and that we would see the day, with developing technology, of the $500 per day cost. Nobody believed him.[1]

For most observers, however, the rate of increase was much higher than expected. This in itself does not mean that the costs were inappropriate, of course, but there also occurred very early in the program the discoveries that (1) the price being paid was still not accomplishing the mainstreaming ideal and (2) a substantial amount of the money was being wasted because of fraud

TABLE 1.—*Growth in Number of Medi-Cal Eligibles**

Year	*Average No. of Eligibles Per Month*	*Percent Increase From Previous Year*	*Medi-Cal Eligibles as Percent of Calif. Population*
1966	1,181,000	..	6.3
1967	1,408,000	19.2	7.3
1968	1,541,000	9.4	7.9
1969	1,744,000	13.2	9.0
1970	2,174,000	24.7	10.9
1971	2,400,000	10.4	11.8
1972	2,312,000	(3.4)	11.3
1973	2,261,000	(2.2)	10.9
1974	2,345,000	3.7	11.2
1975	2,561,000	9.2	12.1
1976	2,679,000	5.3	12.5
1977	2,900,000	7.5	13.2
1978	2,904,000	0.1	13.0

*Source: Table 3 in Derzon RA, Celum CL: The Medi-Cal Program: Strategies for Constraining Costs in the Largest Single Expenditure in the State Budget. Health Policy Program, University of California, San Francisco, December 1979.

TABLE 2.—*Growth in Medi-Cal Expenditures*

	Total Medi-Cal Expenditures			
Fiscal Year	*Amount (Millions of Dollars)*	*Percent Increase From Previous Year*	*Annual Expenditures Per Eligible*	*Medi-Cal General Fund Expenditures as Percent of Total State General Fund Expenditures*
1966-67	$ 804	..	$ 681	8.4%
1967-68*	706	(12.2%)	501	6.4
1968-69	941	33.3	611	8.3
1969-70	1,119	18.9	642	8.8
1970-71†	1,257	12.3	578	10.1
1971-72‡	1,352	7.6	563	10.1
1972-73	1,444	6.8	625	10.0
1973-74	1,734	20.1	767	7.7
1974-75	1,996	15.1	851	8.4
1975-76	2,330	11.7	871	8.4
1976-77	2,653	19.0	984	9.2
1977-78	3,088	16.4	1,065	10.2
1978-79	3,405	10.3	1,173	11.5

*First Medi-Cal cost containment efforts (see text).
†Stronger prior authorization imposed for hospital inpatient care; schedule of maximum allowances for hospital outpatient services; review teams for long term care.
‡Provisions of Medi-Cal Reform Act of 1971 begin to take effect.
Source: Tables 1, 2, and 3 in Derzon RA, Celum CL: The Medi-Cal Program: Strategies for Constraining Costs in the Largest Single Expenditure in the State Budget. Health Policy Program, University of California, San Francisco, December 1979.

and abuse by providers and recipients. Following are excerpts from a report on Medi-Cal prepared in December 1968 by Henry Anderson, a research assistant with the Department of Public Health:

> This laudable concept [patient freedom of choice of providers] is not being well served by Medicaid, in actual practice. In many cases, recipients have scarcely more freedom of choice than they did in the days when they had to go to the outpatient department of the county hospital. A new equivalent of the county hospital has sprung up in the "private sector"—the ghetto physician who enjoys a monopoly in his particular neighborhood. Patients wait in his outer office for hours, just as they used to in the county hospital; they receive care which is every bit as impersonal, and not as good technically as that rendered by the average intern or resident in a county hospital.
>
> In the Surveillance Unit, we consistently found that about 5 percent of the practicing physicians in the state were providing nearly half of all the services in the Medi-Cal program. On the other hand, approximately 50 percent of all the physicians in the state, at the other end of the utilization spectrum, were providing fewer than 5 percent of all the services under the program. Furthermore, in studying the backgrounds of these two groups of physicians, we were struck by an inescapable conclusion: the 5 percent who provided close to a majority of all the care in the program tended to be marginal or submarginal.[3]

Anderson also reported that the Surveillance Unit had identified hundreds of providers who were apparent abusers of the program, based on examination of paid claims data. Even though the Unit had resources to examine only the most extreme cases, Anderson stated that ". . . curbing the abuses we felt we had identified in 1 percent or 2 percent of vendors would have saved the program between $25,000,000 and $50,000,000," which represented 4 percent to 8 percent of the Medi-Cal budget at that time.

We should clarify, as did Anderson in his report, that we believe only a small percentage of providers (or beneficiaries) to be sources of fraud and abuse. The fact remains, however, that the public view of ethics among health professionals has been considerably modified by disclosures of provider behavior in the Medicaid and Medicare programs. There is understandable legislative reluctance to invest more public dollars in these programs until there can be assurance that fraud and abuse are under control. This is fueled by recent allegations that the cost of fraud and abuse is much higher than the 4 percent to 8 percent estimated by Anderson. California's Little Hoover Commission (Commission on California State Government Organization and Economy) has estimated that the figure could be as high as 20 percent (written communication to Governor Edmund G. Brown Jr., et al, September 10, 1979); a recent article in the *LACMA Physician,* by Edward Zalta, MD, concurs with that estimate.[4] There is no evidentiary base for these higher estimates, but they nevertheless represent an increasingly common view of reality.

The Inherent Cost of the Mainstream System

More important than fraud and abuse, in the judgment of the authors, is the fact that under the mainstream ethos the Medi-Cal program buys into the inefficiencies inherent in this country's health care system. The high rate of inflation in the cost of health care generally over the last few years has given medical economists ample opportunity to point out the flaws in that system, as exemplified by the following quotation from Stanford economist Alain Enthoven:

> The main cause of unnecessary and unjustified increase in costs is the complex of perverse incentives inherent in our dominant financing system for health care: fee-for-service for the doctor, cost-reimbursement for the hospital, and third-party insurance to protect consumers, with premiums usually paid entirely or largely by employers or government. This system rewards providers of care with more revenue for giving more and more costly care, whether or not more is necessary or beneficial to the patient. It leaves insured consumers with little or no incentive to seek a less costly health care financing or delivery plan.[5]

In this statement, Enthoven is not talking about Medicaid programs per se, but it clearly applies to Medicaid simply by replacing his phrase "insured consumers" with the phrase "Medicaid beneficiaries." The high rate of increase in Medicaid program costs was to be expected, the economist would say, because demand is unconstrained by the "natural" control of out-of-pocket cost to the consumer. Nor is there any incentive in the system for providers to act in the interest of efficiency; indeed, the efficient provider may simply be losing revenue to inefficient colleagues.

Government Response to Medicaid Costs

The first cost crisis with Medi-Cal occurred when the program was scarcely a year old, and there immediately was a state response that by now represents a very familiar pattern. In August 1967 the state announced emergency regulations to restrict Medi-Cal benefits sharply, citing a projected cost overrun of $210 million for the 1967-68 fiscal year (which at the time represented about 30 percent of the budget). The regulations called for the elimination of certain benefits—for example, chiropractic services, psy-

chiatric services and audiologist services. Other services were restricted: for other than county hospitals, hospital stays were limited to eight days without prior authorization; physician fees were frozen; nonemergency surgical operations were eliminated; optometrists were limited to eye refractions following lens extraction; routine care of nails, corns and calluses was eliminated, and so forth.

The issuance of these emergency regulations was greeted immediately with a temporary restraining order from the Superior Court in Sacramento. Most of the regulations were set aside by a Supreme Court ruling a few months later, but the restrictions on length of hospital stays and physician fees were allowed to stand. Thus, another Medi-Cal tradition was initiated—the use of the courts to decide issues of program administration.

As the cost of Medi-Cal and other Medicaid programs continued to grow at rates in the neighborhood of 15 percent to 18 percent per year, a great many cost containment strategies were attempted. A recent analysis[6] prepared for the California Department of Health Services catalogues approximately 130 cost containment concepts that are either being used in Medicaid programs or have been recommended for use. This variety is obviously too great to discuss in detail in this article, but we can examine the major themes. Table 3 presents a simple taxonomy of Medicaid cost containment approaches. The first level of subdivision separates the concepts that are internal to the Medicaid program—that is, those that can be accomplished by altering the policies and operation of the program itself—from those that are external, in the sense of being dependent on more global modifications in the health care system itself. For cost containment approaches internal to a Medicaid program, there is again a bipartite subdivision: The concepts refer either to reducing the scope of the program or increasing its efficiency.

Reducing the scope of a Medicaid program may mean either reducing the number of people eligible for the program benefits, through modification of the eligibility criteria; or it may mean restricting the benefits available to those who are eligible.

Increasing the efficiency of a Medicaid program means reducing the number of dollars necessary to provide a given scope of benefits to a given population. As indicated by the table, cost containment concepts in this area generally relate to either reducing the need for care among the eligible population, reducing rates of payment, implementing administrative interventions to avoid (either prospectively or retrospectively) inap-

TABLE 3.—*Taxonomy of Medicaid Cost Containment Concepts*

Concept Category	*Examples*
I. Internal—can be implemented within the program	
A. Reduction in scope of program	
1. Reduce number of eligibles	Eliminate optional aid categories. Increase beneficiary share of cost. Require work registration as condition of eligibility.
2. Reduce scope of benefits	Remove outpatient psychiatric services. Limit acute hospital inpatient days to 21 per beneficiary per year.
B. Increase program efficiency	
1. Constrain provider rates	Freeze physician payment rates. For selected surgical procedures, pay outpatient rate only.
2. Reduce need for care	Implement program of secondary prevention such as hypertension control.
3. Administrative interventions	Require prior authorization. Implement automated surveillance system. Use detailed edits and audits during claims processing.
4. Alternative delivery systems	Contract with HMO's. Contract selectively with hospitals, choosing efficient facilities.
II. External—require changes in health care system generally	
A. Develop more efficient health care delivery system	Encourage development of HMO's. Implement "consumer choice" economic theory.
B. Reduce poverty	Job training programs.
C. Reduce illness	Free family planning for low income persons. Traditional public health measures.
D. Spread actuarial risk	Require broader and longer coverage with employer policies. Implement subsidized health insurance for low income persons.

TABLE 4.—*Distribution of Medi-Cal Costs by Category Eligibility*

Eligibility Category	*Percent of Health Care Costs*
Public Assistance categories	
1. Aid to Families with Dependent Children	22.4
2. Disabled	25.1
3. Aged	21.8
4. Blind	0.7
Medically Needy (categorically linked)	
5. Aid to Families with Dependent Children	6.0
6. Disabled	2.1
7. Aged	2.1
8. Blind	0.0
Medically Indigent (not categorically linked)	
9. Medically Indigent Children	3.7
10. Medically Indigent Adults	17.4

Note: The Medically Needy categories (lines 5-8) and Medically Indigent Children (line 9) are optional categories under federal law. Federal financial participation (FFP) is available if a state elects to invest in coverage of these categories. The Medically Indigent Adult category (line 10) is not covered by the federal Medicaid law; all costs are paid by the state of California.

propriate costs or attempting to shift to alternative health care delivery systems that in themselves are believed to be more efficient.

The shift to more efficient delivery systems is also an external strategy, under the reasoning that Medicaid will benefit from such developments as increasing the number of health maintenance organizations. The other cost containment approaches that would be classified as external to the Medicaid program are generally aimed at preventing people from developing the need for the program's benefits. Since people become eligible for a Medicaid program by being either poor, or marginally poor and sick, these concepts fall readily into the three classses of attempting to increase the health status of the general population, reducing the likelihood of poverty and using alternatives to tax funding for spreading among the working population the fiscal risk of illness among the marginally poor.

Cost Containment Through Reducing Program Scope

In the remaining discussion we will restrict our attention to the cost containment concepts internal to Medicaid programs, leaving for other forums the consideration of global modifications in the country's health care system or economic system (or both). We first consider program cost reduction through restrictions in scope—eligibles or benefits.

Table 4 shows how the health care expenditures in the Medi-Cal program are distributed among categories of eligibility. Note that the Medi-Cal eligible population is really a set of subpopulations that differ from one another demographically and in terms of health care need. Every Medicaid program must cover persons who are receiving cash grants under either a state Aid to Families with Dependent Children (AFDC) program or the Federal Supplemental Security Income program for the aged, blind and disabled. States may elect to go beyond these mandatory categories to extend Medicaid eligibility to the medically needy—persons who meet the categorical criteria (families with dependent children, and the aged, blind or disabled) but who have income above the cash grant limit. (Persons with income more than 33⅓ percent above the cash grant limit can only become eligible by spending the excess income on health care—a process commonly known as "spending down.") The federal medically needy eligibility criteria also include persons under 21 and families which do not meet AFDC criteria, but do meet the other medically needy income level criteria.

A very potent form of cost containment for a state is simply to eliminate all of the eligibility categories not absolutely required by federal law. California has in the Medi-Cal program the broadest scope of eligibility permitted by federal law; indeed, Medi-Cal includes a Medically Indigent Adult eligibility category which goes beyond the federal limits, and consequently receives no federal financial participation. California could save approximately 41 percent of Medi-Cal costs to the state general fund simply by eliminating the eligibility categories that are optional according to federal standards.

The temptation to do this has been resisted throughout the history of the Medi-Cal program, in spite of strong cost containment pressures. The major reason is that this form of cost containment simply means shifting the burden of indigent health care to other levels—county or city governments, providers or individual patients. Moreover, this affects those who are medically indigent —meaning both poor and sick, the persons most in need of medical assistance. Such a change would contradict the essential mission of a Medicaid program, which is to assure that limited financial resources are not a barrier to obtaining necessary health care.

The other approach to reducing Medicaid costs by reducing scope is through restriction of benefits. Table 5 shows how the Medi-Cal health care

TABLE 5.—*Medi-Cal Costs by Category of Service, Fiscal 1978-79*

Category of Service	*Percent of Health Care Costs*
1. Hospital inpatient	38.4
2. SNF and ICF	20.8
3. Physician	17.1
4. Outpatient clinics	5.7
5. Prescription drugs*	5.5
6. Dental*	3.7
7. Professional, other than physician*	3.7
8. Short-Doyle*	2.9
9. Other*	2.1

*Most of the services included in these categories represent services not required of a state Medicaid program by federal law, but services in which there will be federal financial participation if offered by the state. Most of the services covered in the categories in lines 1-4 are mandated by federal law for any state that operates a Medicaid program.

SNF=skilled nursing facility
ICF=intermediate care facility

dollar is distributed among categories of service. Again, federal law requires that the Medicaid program offer certain types of health care service, with others available at state option. An obvious cost reduction alternative for a state with more than the federally mandated services, as California has, is to eliminate the optional services. Table 5 shows that this would reduce the Medi-Cal cost by approximately 15 percent. However, a third of that 15 percent represents outpatient pharmaceuticals. Even though this is optional by federal standards, it would be unwise to eliminate it from the program, since there would undoubtedly be a shift to use of higher-cost modalities of treatment.

States may also place limits on the extent to which mandatory services are covered. For example, the Oregon Medicaid program presently covers only 15 days of acute inpatient hospital care per year for each beneficiary. This is an approach that has been resisted in the more liberal Medicaid programs because it has exactly the same effect as restricting eligibility—the people most in need of medical assistance are the ones who are cut off when their benefits are exhausted. The financial burden for their care is simply shifted from the state level (where there is federal financial participation) to either local government, private sector charity or the individual person.

Cost Containment Through Increasing Program Efficiency

Since cost containment by reducing the scope of a Medicaid program is inimical to its fundamental purpose—providing necessary health services to those who cannot afford them—considerably more emphasis has been placed on attempts to make the Medicaid program more efficient.* In this context, increasing efficiency means reducing the number of dollars needed to provide a specified scope of benefits to a beneficiary population of specified size and eligibility category mix.

In considering the "efficiency" approaches to cost containment, it is especially important to note that the nature of government reaction to the escalating costs of Medicaid programs has been keyed directly to the nature of the "mainstream" health care system. In particular, the government cost controls are largely determined by the reimbursement methods that the majority of providers insist upon.

For example, when Medicaid was originated, the hospital industry successfully lobbied for "reasonable cost" reimbursement as a federal requirement for inpatient care. Given this as the essential reimbursement method, when a Medicaid program is faced with limited financial resources, it is both rational and inevitable that the following cost control measures will be taken with respect to hospital inpatient care:

- Prior authorization of access to hospital inpatient care, which is the most expensive type of service in a Medicaid program. As noted above, this was begun in Medi-Cal in 1968 (for stays beyond eight days in noncounty hospitals). It was made more stringent in 1970, by requiring prior authorization for all nonemergency hospital admissions and emergency hospital stays beyond three days.
- Limitations on length of hospital stays without additional authorization. This was started in Medi-Cal in 1970, and now is a common element of the "concurrent review" conducted by Professional Standards Review Organizations across the country.
- Careful scrutiny of cost accounting methods, and the method of allocating total hospital costs to the Medicaid patients.
- Reinterpretation of "reasonable cost" to mean reasonable *amount* of cost as well as reasonable type of cost. This means judging reasonableness in terms of costs in similar institutions, and increases in "input" costs for the hospital in-

*It should also be noted that those states that have Medicaid programs of limited eligibility and benefits still tend to experience the same rate of increase in costs as the more liberal programs, even though the dollars expended per beneficiary will be less. The motivation to increase program efficiency is thus as strong in the restricted programs as in the liberal ones.

dustry; and evaluating medical necessity as an element of reasonableness. For selected hospitals, Medi-Cal now sends in multidisciplinary teams for the retrospective audits, which include medical personnel as well as fiscal auditors.

• Attempts to limit participation to efficient facilities. In 1979 the administrators of Medi-Cal prepared a legislative initiative—subsequently defeated through the strong opposition of the industry—to obtain authority to contract selectively with hospitals.

Most physicians prefer to be reimbursed on the basis of usual and customary fees for each service rendered. Under federal regulations, Medicaid programs have more freedom to restrict physician payment levels than they do hospitals for inpatient care—the major constraint is that states cannot pay physicians more than they receive from Medicare. Under cost containment pressure, then, it is to be expected that states will take the following actions:

• Reduce physician fees, or freeze them over long periods of time in spite of general inflation. As noted above, this was part of the Medi-Cal reaction to the first cost crisis, in 1968. Medi-Cal rates for physicians presently average about 55 percent of usual and customary charges.

• Implement sophisticated computer systems to catch physicians who attempt to compensate for the low fees by bringing patients back for multiple visits, performing (or at least billing for) injections and laboratory tests on each visit, or similar inventive techniques for maintaining revenue. Anderson had this capability back in 1967 and 1968; it is now a part of the "Surveillance and Utilization Review" system for which the federal government pays states a bonus to implement.

• Introduce computerized edits into the invoice processing system itself, which are intended to apply a degree of medical judgment to each service billed by a physician. The contemporary automated invoice processing systems used in Medicaid programs, for example, will check on whether the procedure billed was justified by the diagnosis; whether the procedure was appropriate for the age and sex of the patient; whether the frequency of the procedure was appropriate. Some of these edits are mundane and obvious—such as no more than one appendectomy per patient; others may be more judgmental—such as no hysterectomies in women under age 25. (The computer does not make final judgments on these matters. Instead, claims are referred to medical personnel for review.)

• Send state-employed investigators into physician offices, in the guise of Medicaid beneficiaries, as the ultimate check on physicians suspected of fraud or abuse. This has not yet happened in California, primarily because state law does not permit it, but has been done in other states.

This last statement illustrates the extreme we have reached in Medicaid programs, as government and providers each try to compensate for the behavior of the other. The authors largely agree with Dr. Zalta, a strong critic of Medi-Cal, when he states the following with respect to fraud and abuse:

> The present system has spawned this and continues to nurture it. Inadequate reimbursements and higher litigation rates make it more difficult for hospitals and physicians to accept the Medi-Cal patient. The deserving poor are thus forced into a "mill" where manipulators milk the system for all its worth.
>
> Even some honest practitioners delude themselves into "rationalizing" fraudulent behavior by adding on extra services. These practitioners have had so many legitimate claims rejected by the state that they feel justified in "beating the system."[4]

We conclude that if the fee-for-service, cost-plus system has inherent perverse economic incentives, as Enthoven claims, the attempts by government to control Medicaid costs have been equally perverse. States have developed extensive procedures for second-guessing the professional judgments of physicians, and for probing the fiscal and medical records of physicians, hospitals and other providers. These invasive techniques, together with low payment levels, drive physicians out of the program, reduce beneficiary access to physician care, and force beneficiaries into use of hospital emergency rooms—usually in county hospitals, the provider of last resort. Quality suffers, costs continue to increase, and the state in turn invents new ways to intervene in the health care process. This could hardly be the vision of mainstream medicine that stimulated the creation of Medicaid.

The Search for Alternative Systems

It was to be expected, then, that government would seek alternatives to the fee-for-service, cost-plus system as the method of health care delivery for Medicaid. After all, for many years in California there have been millions of people

receiving care through organized delivery systems such as Kaiser Health Plan and Ross-Loos, at considerable saving over the usual indemnity insurance plans.

Medi-Cal first experimented with prepaid health care in 1968. By 1971 the policy decision had been made that the best solution to cost containment would be contracts with prepaid health plans (PHP's). The Medi-Cal Reform Act of 1971 laid the foundation for a carrot-and-stick approach to increasing the reliance on PHP contracts. The "stick" was the implementation of more stringent prior authorization and service limitation controls on fee-for-service Medi-Cal—the types of controls we have just discussed. The "carrot" was the easing of certain legal barriers to PHP contracting, plus aggressive administrative action to encourage contract proposals.

The following quotation from a staff policy paper of 1972 communicates the enthusiasm with which this new alternative was pursued:

> A decision has been reached in California public policy —*Prepayment in the delivery of health care offers the best solution to the joint problem of cost control and quality of care.* [Emphasis in original.]
>
> And most significantly, prepayment to providers, whether they are aware of it or not, offers a means for them to retain control of their fiscal and professional destinies, to bring about modern management and organization in the delivery of care, and to foster the kind of care that is most meaningful to the true health and well being of California's people. . . . the change now happening in California is not a minor event but an avalanche which will find echoes and parallels across the nation.[7]

We know now, of course, that there were flaws in the PHP theory. Just as at the inception of Medicaid few people had anticipated such phenomena as "Medicaid mills," so at the inception of the PHP program few people expected the degree of abuse that resulted from stimulating entrepreneurial instincts through prepaid contracts. The financial incentive of such contracts is to sign up as many healthy Medi-Cal beneficiaries as possible, and then to minimize costs by minimizing service levels. It had been expected that this incentive would be largely offset by professional ethics, together with a modest amount of state monitoring, but experience soon showed that prepaid care was as much susceptible to abuse as fee-for-service care. And because beneficiaries were "locked-in" to a single source of care, the impact of such abuse was specially adverse.

It is still not clear the extent to which the problems of the PHP program were specific to a few notorious contractors, or were spread through much of the program. What *is* clear is that the state had insufficient monitoring capability to discern where the real problems lay—beyond the obvious scandals—and to satisfy the public that they could be controlled. This has been rectified (at least to the extent that there have been no major scandals for the last four years), through administrative action and new legislative requirements at both the state and federal levels.

It is easy, because of the scandals in the early years of California's PHP program, to overlook the inherent advantages to both providers and the state in this form of health care delivery. These are the following:

- Efficiency. The evidence from a variety of settings is that PHP's can provide a comprehensive spectrum of benefits at costs ranging from 10 percent to 40 percent less than the fee-for-service system.[8] For Medi-Cal itself, the savings have averaged about 15 percent (Rigby Leighton, "Evidence for Cost Reduction Impact of PHP Contracts," internal memorandum, California Department of Health Services, April 5, 1978). The Michigan Medicaid program, which now has a higher percentage of its beneficiaries under prepaid contracts than any other state, reports savings on the order of 15 percent to 20 percent. There is no other single cost containment technique which can produce this degree of saving in a Medicaid program, short of severe restrictions on eligibility.

- Professional autonomy. The major advantage from the provider perspective is freedom from the controls applied to fee-for-service: prior authorization, computerized edits applied to each service rendered, and the retrospective "surveillance and utilization review" of patterns of service rendered. There are requirements for internal quality assurance procedures, and periodic medical audits are conducted to assure that such procedures are effective, but these are oriented toward the total system of health care rather than the second-guessing of individual judgments that occurs wth fee-for-service claims.

- Legal obligation to serve beneficiaries. From the beneficiary perspective, the major advantage is guaranteed access. Unlike fee-for-service providers, the PHP contractor takes on a legal obligation to serve those beneficiaries who elect to enroll. The early PHP program experience made

it clear that there needs to be monitoring to assure that this obligation is satisfied, but there is not even the basis for such monitoring with fee-for-service physicians.

There are numerous other advantages that could be attributed to PHP's, under the same theory that is held by many to apply to Health Maintenance Organizations: incentive for preventive medicine, improved case management through centralized record-keeping and the like. These putative advantages are more arguable than the three cited above, however, which are sufficient in themselves to account for the survival of the California PHP program in spite of its early scandals, and the current federal emphasis on encouraging the spread of Health Maintenance Organizations.

The Freedom of Choice Dilemma

Even though the PHP program was a conscious attempt to move away from the fee-for-service, cost-plus system, it still could be construed as a mainstream option. Prepaid care is certainly a well-established option in California—currently about 20 percent of the people not covered by Medi-Cal or Medicare belong to Health Maintenance Organizations. Also, the program did not deprive Medi-Cal beneficiaries of the freedom to choose a fee-for-service identification card.

However, the PHP program obviously did not meet the cost containment objectives of its founders, who had anticipated that within a few years most beneficiaries would be covered under such contracts. A Medi-Cal policy paper developed in 1974, titled "The Medi-Cal Program, A New Direction," analyzed the problem this way:

> Although 56 individual PHP's are operating in California today, the expansion of this concept statewide has been hindered by the competitive environment and the stringent marketing procedures necessitated by the federal "freedom of choice" requirements. As a result the vast majority of beneficiaries continue to receive their medical care via the conventional fee-for-service system.[9]

(The policy paper failed to note the adverse influence of active campaigns by welfare rights advocates and eligibility workers to keep beneficiaries out of PHP's, and the legislative and congressional investigations of the program.)

The "New Direction" paper proposed to overcome these obstacles by contracting with a single Organized Health Delivery System (OHDS) in each geographical area. To the extent possible, the OHDS selected would have the capability of providing all medical services from a centrally located facility. Reimbursement would be through either prepaid capitation in the manner of PHP's (the preferred alternative) or prospective budget approval.

In terms of policy, the most significant aspect of the proposal was the abandonment of beneficiary freedom of choice, one of the cornerstones of the mainstream medicine ideal. The proposal stated "Each beneficiary within a designated area would be assigned to the selected organization for all his health needs." This recommendation was justified with the following two arguments:

- Beneficiary welfare.

> The availability of routine and emergency care would be guaranteed to each beneficiary. Currently, due to the increasing specialization, a beneficiary is often referred to several providers, often at diverse locations, for the treatment of his illness. A centrally located facility would have all specialties available, thereby eliminating both costly referrals and duplication of effort. The OHDS concept would permit consolidation of a beneficiary's medical records, the development of beneficiary medical profiles, and assure continuity of care.

- Economic necessity.

> The OHDS concept appears to be the only viable alternative to massive tax increases which will be necessary to continue the present fee-for-service system.

The "New Direction" paper estimated that the OHDS concept could reduce Medi-Cal expenditures by 20 percent.

The OHDS concept never became official Department policy. Indeed, it was completely rejected by the Health Department leaders who came into office with the new Brown administration in 1975.* Rather than allowing cost containment to be the dominant theme, the new administration removed many of the prior authorization controls in fee-for-service Medi-Cal and launched an extensive reformation of the PHP program. The number of PHP contractors was cut in half by the end of 1975, and halved again by the end of 1976.

Medi-Cal costs increased by 12 percent between fiscal 1974-75 and 1975-76, and 19 percent between 1975-76 and 1976-77. Yet "massive tax increases" were not necessary; indeed, the state enjoyed a multibillion dollar surplus. At this point, the OHDS concept paper—the first explicit critique of the practicality of mainstream medicine for Medi-Cal—seemed to represent little

*The concept is by no means dead, however. The state of Arizona recently announced a cost containment strategy for its indigent medical care program, based on assignment of beneficiaries to either HMO's or an individual primary care physician.[10]

more than self-serving hyperbole when it asserted that "At some point the taxpayer either cannot or will not bear the awesome increases in the existing Medi-Cal program." This statement was to be prophetic, as we will discuss presently.

The Taxpayer Revolt

Publicly funded health care was not the explicit target of the California taxpayer revolt that began with Proposition 13, but it has been, and will continue to be, a victim. The immediate impact of Proposition 13 itself, which passed in June 1978, was to reduce property tax revenue to counties. This in turn sharply reduced the ability of counties to operate health facilities (about 30 percent of Medi-Cal hospital inpatient and outpatient care was in county facilities), to meet their legal obligation for health care of the indigent not eligible for Medi-Cal, and to meet the "county share" obligation for Medi-Cal program costs. Prior to Proposition 13, the counties had been contributing approximately 12 percent of the Medi-Cal budget.

The immediate fiscal impact of Proposition 13 on the counties was resolved by using surplus state funds to supplement lost property tax revenue. The county share of Medi-Cal cost was eliminated and counties were given state funds to support both public health services and personal health services to the indigent. For the moment, publicly funded health care was impaired, but not disastrously so.

A secondary effect of Proposition 13 was the attempt of politicians to respond to its "message." All agencies of California government were asked to propose 10 percent budget cuts for the 1979-80 fiscal year. Since the Medi-Cal program budget had been growing at an average annual rate of 15 percent per year, the request for a 10 percent *cut* was in effect a requirement for an immediate 25 percent cost containment effect.

Beverlee Myers, Director of the Department of Health Services, convinced the Governor that Medi-Cal should not be subjected to an immediate 10 percent cut; that instead, a plan for restructuring the Medi-Cal program would be developed with the objective of producing a long-range 10 percent cost containment effect. The Medi-Cal Restructuring Plan of 1979 was developed,[11] with the following elements:

- Increased reliance on prepaid health plans and other forms of organized health systems (but not the franchising envisioned by the 1974 OHDS proposal, and without removing of beneficiary freedom of choice).
- Special contract relationships with county health systems, with particular emphasis on stimulating county-operated PHP's.
- Requiring beneficiaries to make an explicit, informed choice of method of receiving benefits (PHP, fee-for-service, county system and so forth) at time of eligibility determination.
- The development of contracts with high-volume providers, including risk-sharing and other incentives to efficiency.
- Selective contracting with hospitals for inpatient care, to minimize the program's exposure of the cost of the excess hospital capacity which is prevalent in California.
- Strengthening of fee-for-service controls, but without return to the service limitations imposed pursuant to the Medi-Cal Reform Act of 1971.

The Restructuring Plan represented a clear intent to move away from almost exclusive reliance on the fee-for-service, cost-plus system toward (1) more extensive use of organized health systems and (2) a system of contracting with providers that would allow the Department to emulate the functions of organized health systems. Beneficiary freedom of choice would be preserved, but the hope was to provide beneficiaries with more efficient options for receiving Medi-Cal benefits than was represented by fee-for-service.

The legislative proposal necessary to implement many features of the Restructuring Plan, introduced as Senate Bill 716, was strongly opposed by the hospital and medical industry. The principal argument used against the bill was that it would do away with mainstream medical care for the poor. Following is an excerpt from the statement of Paul Ward, writing as President of the California Hospital Association (CHA):

> CHA opposes SB 716 because it will result in a return to the separate system of care for the poor that existed prior to 1965—a system that was underfunded, overcrowded and inadequately supported to meet the health needs of the poor. The legislature decided in 1965 that there should not be a separate system for the poor, that the poor should have access to the same care provided the remainder of our society and we trust that this legislature will not want to return to the dual system of the past. (Written communication to the Honorable John Garamendi, Chairman, Senate Commission on Health and Welfare, April 2, 1979.)

The California Medical Association (CMA) had a similar viewpoint:

Medi-Cal beneficiaries will be forced to return to something similar to the county hospital system, an institution of the past notorious for its poor quality of care provided to indigents. . . . The anonymity suggested by the county health care system could severely hinder and possibly eliminate the trust and confidence of the established physician-patient relationship now available to the Medi-Cal recipient through the fee-for-service system. (Written communication from George F. Cate, Associate Director, Division of Government Relations, California Medical Association, to members of the Senate Health and Welfare Committee, May 22, 1979.)

It is clear that CHA and CMA still considered mainstream health care a feasible objective for Medi-Cal. Indeed, the CMA statement seems to imply that it is "now available to the Medi-Cal recipient through the fee-for-service system." CHA did not offer an alternative plan for Medi-Cal cost containment. CMA did support,[12] as its cost containment alternative to SB 716, a bill that had as one of its provisions the raising of Medi-Cal physician payment rates to Medicare levels. That would have been a 45 percent increase in physician reimbursement, adding $400 million per year to Medi-Cal costs.

SB 716 was defeated, thus meeting the same fate as all recent California legislation aimed at containing health care costs. The Department continues to pursue the elements of the Medi-Cal restructuring strategy, to the extent they are enabled under existing statute, which is primarily under limited pilot project authority.

The Coming Crisis

California's Proposition 13 proved to be only the first round in the taxpayer revolt. It was emulated in variations in several other states, either through voter initiatives or legislative action to preclude voter initiatives. In November 1979 the California electorate passed Proposition 4, the Gann Initiative, setting an annual increase limit on government appropriations. The June 1980 California ballot carried Proposition 9—which was commonly known as either "Jarvis II" in reference to its sponsor or "Jaws II" in reference to the impact it would have had on state revenue from personal income taxes.

Although Jarvis II failed to pass, the prospect of its passage was taken seriously by California state government. In anticipation of the worst, all state agencies were requested to prepare contingency budgets with 30 percent fewer dollars in them than the fiscal 1980-81 budget then before the legislature.

The failure of Jarvis II brought temporary relief, but it is clear that the fiscal stress on Medi-Cal can only become stronger in the next few months and years. The safest prediction to make about the types of cost containment strategy that will be pursued is this one: All of the above. If Medi-Cal is indeed expected to live on significantly fewer dollars than it has in the past, then all alternatives must be considered.

Note that the most extreme proposal advanced thus far for increasing the efficiency of the program—the organized health delivery system proposal of 1974, which would have removed beneficiary freedom of choice—was estimated to save 20 percent, and that was very likely an optimistic estimate. If Jarvis II is indicative of the degree to which tax revenues may be reduced in the future, either through subsequent voter initiatives or legislative action to forestall such initiatives, then it will be necessary to reduce the scope of the Medi-Cal program, by cutting eligibles or benefits (or both).

The dilemma this presents for California is that the counties, although legally the providers of the last resort, are ill-prepared to take up the slack, because of the impact of Proposition 13. The counties are already receiving a state subsidy averaging more than 40 percent of their costs for both public health programs and personal health care of the indigent not presently eligible for Medi-Cal, and that subsidy itself will be in jeopardy if there is substantial reduction in health care expenditures.

Reassessing the Mainstream Ethic

In the Paul Ward interview we have quoted above, Mr. Ward was asked whether he still felt the ideal of mainstream medicine for the poor was realistic. His answer was not explicit, but it was pessimistic:

It's a change of attitude. It is said that the life of an issue in American politics is seven years. Health ran its course as an acceptable issue; people became bored with it and tired of it. Their interests turned to other issues: environment, energy. So they said, "We're going to have to put the brake on health expenditures."[1]

At the outset of this article we quoted a letter from the Western Center on Law and Poverty to Governor Brown (December 12, 1978), which put the matter plainly: "We can no longer afford a private, fee-for-service system." This may sound like a typical right-wing, antiwelfare statement, but in fact the letter was signed by 45 representatives of local legal aid societies, who are among

the strongest advocates for the rights of the poor. The letter was sent in protest of the Governor's request, following the passage of Proposition 13, that a plan be developed to cut the Medi-Cal budget by 10 percent. The message of the letter was that county health services, the providers of last resort for the poor, must be sustained: ". . . It is obvious that further cuts in health care and a failure to assist county health care systems with State funds will mean more suffering, maiming and death."

The significance of the Western Center statement is that it signals recognition, by those most concerned with the plight of the disadvantaged, that simplistic adherence to the "mainstream medicine" principle is unworkable under current cost containment pressures. These advocates for the poor see the fundamental issue as not whether the poor will have access to mainstream care, but whether the poor will have access to *any* care.

There seems little doubt that we are facing a time when it is not only opportune, but absolutely necessary, to rethink our ideals and our strategies. There is no need to abandon the objective of providing all persons an equitable opportunity for good health, regardless of financial status. But we do need to be prepared to abandon our shibboleths in the interest of finding a more realistic way to reach that objective.

This is not a new concept. Anderson saw it clearly in 1968, when he concluded a discussion of the fallacy of the mainstream ideal with the following observation:

> The proper standard for evaluating public medical care programs is not what was done at some other time, or is being done at some other place, but what it is possible to do here and now, given the amount of money we have to spend and given what we know about the art and science of preventing disease, curing it and prolonging life. Or, to put it another way, the most fitting goals and yardsticks of the programs are not extrinsic but intrinsic: what is happening to the people being served by these programs.[3]

Summary

The credit card approach to funding health care for the poor carried with it the economic seeds of its own destruction, exacerbated by the incentives of the reimbursements demanded by most health care providers. We have allowed an unthinking preoccupation with mainstream medical care as a philosophical ideal to distract us from the more fundamental task of building a system of health care that can serve the financially disadvantaged at a cost tolerable to our society.

Publicly funded health care is facing a growing economic crisis because of the taxpayer revolt, but publicly funded health care had a part to play in stimulating that revolt. Although the fiscal impact cannot be predicted with certainty, it is highly likely that a wide variety of cost containment strategies—including those that have thus far been unpleasantly invasive of the professional functions of physicians and other health care providers—will be called into play in an effort to maintain the integrity of these programs. A time of crisis is also a time of opportunity. In the 15 years of the Medicaid program history we have learned some hard lessons in medical economics, ethics, and politics. We have a considerable amount of experiential data with which to rethink our premises and restructure our strategies.

Our rethinking must center on the fact that resources are limited. Rationing of health care is not avoidable; the issue is how and by whom it will be accomplished. This is not to say that the health care industry should not fight for its share of society's resources, particularly in the interest of the disadvantaged. But it would be foolish to base our program's operational strategies on pious philosophies that would require unlimited supply to implement. This is the lesson we are about to learn from the taxpayer revolt, as its impact becomes felt in publicly funded health care programs.

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Special Article

Refer to: Heckman JR, Jones MW: Runaway costs in Medi-Cal—A myth. West J Med 132:562-566, Jun 1980

Runaway Costs in Medi-Cal—A Myth

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An analysis of increases in Medi-Cal expenditures to their present level, more than $4 billion a year, shows them to be attributable largely to changes in eligibility and scope of benefits. The actual costs of providing care have risen at a relatively modest rate. If in fact costs are to be lowered from present levels, public policy makers must make important decisions concerning program changes which transcend merely altering payment and delivery methods.

FIGURES USED and statements made during the past several years by the California Department of Health Services concerning increases in the cost of California's Medicaid program—Medi-Cal—purportedly show that it has become a runaway program. Such conclusions have led the state administration to question whether the program can continue to be financed on a fee-for-service basis.[1,2]

Indeed, the total cost of care under Medi-Cal rose from approximately $1.4 billion to $2.9 billion between 1973 and 1978, and has continued to increase since that time. Ostensibly more shocking, the program's total cost was a relatively meager $306 million in the first year of its implementation, 1966. Using this as a base, the increase over the 13 years for which hard figures are available amounts to approximately 850 percent.[3-5] These apparent aberrations need to be put into proper perspective, and the following analysis attempts to do so.

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First, the use of any figures for years before 1973 for purposes of analyzing trends is totally unrealistic. For one thing, total eligibility figures doubled between 1966 and 1973. More important, however, was the disproportionate increase in numbers of "noncategoric" recipients (that is, the Medically Needy and Medically Indigent).[6] Indeed, the Medically Indigent category was not introduced into Medi-Cal until late 1971, and eligibility figures do not appear until the 1972 reports. For the Medically Needy, the first figure, for 1966, was just 68,000 eligibles, or 5.8 percent of the total program. In 1978 this category accounted for 331,000 persons—an increase of almost 400 percent. If the 410,000 persons in the Medically Indigent category were added to this, the increase in this considerably more expensive type of beneficiary between 1966 and 1978 would amount to almost 1,000 percent. Conversely, the number of relatively low-cost Public Assistance program recipients increased by just 83 percent during that same period. Thus, it is ludicrous to discuss cost increases since the program was initiated without indicating the major changes that took place in eligibility during its early years. It

should also be noted that figures beyond 1978 have not been used in this article, because they are insufficiently detailed.

Since 1973, however, the only major program changes have been inclusion of patients receiving renal dialysis, which in the aggregate do not represent a substantial portion of total expenditures, and some slippage in the number of enrollees in prepaid health plans. The year 1973, then, can serve as a realistic base year for evaluating the cost of the program, and Tables 1 through 5 use data from 1973 to 1978 for this purpose.

As can be seen in Table 1, the total number of eligibles increased by 29.3 percent between 1973 and 1978. Within specific programs, however, rates of change have differed dramatically—an increase of 13.6 percent in Public Assistance compared with 159.0 percent in the Medically Needy program and 171.3 percent in the Medically Indigent program. The importance of these disparities becomes evident when one observes the considerable differences in the average monthly payment per eligible under each of these three major programs. In 1978 the differences ranged from $61.52 per month in the Public Assistance program to $186.31 per Medically Needy eligible. When the figures for the three programs are aggregated, the total monthly payment per eligible grew from $54.65 in 1973 to $85.37 in 1978, or 56.2 percent. However, this is due more to the composition of the types of beneficiaries than to increases within each category. While the slowest growing program, Public Assistance, showed a per eligible cost increase of 63.7 percent, the faster growing Medically Indigent program showed a cost increase of just 33.2 percent and the Medically Needy program, a decrease of 11.3 percent.

Furthermore, there were important differences in the categories *within* the specific programs. As seen in Table 2, the major growth among the four categories of Public Assistance was in the number of disabled: 69.6 percent (from 205,000 to 347,000). The average monthly payment for disabled beneficiaries was $139.59 in 1978 compared with $61.52 for all Public Assistance beneficiaries. And the disabled now constitute 17.1 percent of the overall program, compared with just 11.7 percent five years earlier.

Tables 3 through 5 employ actual figures from 1973 or 1978 (or both) and, using varying hypotheses, show whether there has been an inordinate increase in the cost of medical services under the fee-for-service portion of the Medi-Cal program.

Table 3 compares actual annual expenditures under the program for the three primary types of beneficiaries—Public Assistance, Medically Needy and Medically Indigent—with figures that might have resulted if per eligible cost had risen between 1973 and 1978 at the same rate as did the Medical Care Index (10.1 percent) and the Consumer Price Index (8.2 percent) in California. The two index figures are taken from data used in Illustration 2.7 of the recent Department of Health Services study concerning Medi-Cal, entitled "Looking for the Monster."[2]

Had payments per eligible beneficiary increased by the 10.1 percent per year inflation rate in medical care prices in California, total program cost would have risen to well over $3.5 billion, rather than the $2.8 billion actually spent on

TABLE 1.—*Number of Persons Eligible for Medi-Cal Benefits and Monthly Payments Per Eligible, by Program, 1973-1978*

	Number Eligible					*Monthly Payment Per Eligible*				
		Program†					*Program†*			
Year	*All Programs**	*PA*	*MN*	*MI*	*RD*	*All Programs*	*PA*	*MN*	*MI*	*RD*
1973	2,260,800	1,794,248	127,957	151,168	..	$54.65	$37.59	$209.95	$ 91.75	..
1974	2,345,300	1,764,586	156,607	182,632	..	59.07	41.83	196.82	97.00	..
1975	2,560,800	1,874,421	190,203	224,296	22	63.11	46.79	174.64	104.96	..
1976	2,697,300	1,998,254	205,018	262,163	39	67.32	49.94	182.88	109.25	$1,025.64
1977	2,899,900	2,032,439	310,081	395,512	57	77.60	57.60	167.34	110.33	1,033.47
1978	2,922,300	2,037,609	331,361	410,179	77	85.37	61.52	186.31	122.21	641.12
Change, 1973-78 ..	+29.3%	+13.6%	+159.0%	+171.3%	..	+56.2%	+63.7%	−11.3%	+33.2%	..

MI = medically indigent; MN = medically needy; PA = public assistance; RD = renal dialysis

*Also includes prepaid health plan enrollees
†Fee-for-service program only

TABLE 2.—*Public Assistance Programs: Eligibility and Monthly Payment Information, by Specific Category, 1973-1978*

	Specific Category								Average Monthly Payment			
	Aged		Blind		Disabled		Families		Aged	Blind	Disabled	Families
	Number	Percent	Number	Percent	Number	Percent	Number	Percent				
1973	290,799	16.2	13,766	0.7	204,931	11.7	1,284,771	71.6	$33.12	$ 67.13	$112.24	$26.37
1974	304,927	17.3	13,416	0.8	234,017	13.3	1,212,226	68.7	37.34	71.10	112.61	28.98
1975	322,147	17.2	12,666	0.7	281,168	15.0	1,258,439	67.1	42.45	74.62	117.19	31.89
1976	328,988	16.5	12,682	0.6	322,545	16.1	1,334,039	67.3	45.55	80.69	120.30	34.29
1977	321,460	15.8	12,519	0.6	332,519	16.4	1,365,942	67.2	52.06	93.89	134.81	39.77
1978	323,461	15.9	12,644	0.6	347,496	17.1	1,354,009	66.5	57.72	106.30	139.54	41.97
Change, 1973-78	+11.2%	−1.9%	−8.2%	−14.3%	+69.6%	+46.2%	+5.4%	−7.1%	+74.3%	+58.3%	+24.3%	+59.2%

TABLE 3.—*1978 Medi-Cal Fee-for-Service Expenditures, Actual and Hypothetical (If Cost Per Eligible Had Risen at MCI or CPI Levels*)*

	Number Eligible, 1978	Payments Per Eligible (Monthly)	Total Payments (Annual) (000)
Actual (1978):			
PA	2,037,609	$ 61.52	$1,504,266
MN	331,361	186.31	740,829
MI	410,179	122.21	601,558
TOTAL	..	..	2,846,653
Using MCI:			
PA	2,037,609	60.81	1,486,884
MN	331,361	339.67	1,350,641
MI	410,179	148.44	730,644
TOTAL	..	..	3,568,169
Using total CPI:			
PA	2,037,609	55.75	1,363,158
MN	331,361	311.35	1,238,031
MI	410,179	136.06	669,707
TOTAL	..	..	3,270,896

CPI: Consumer Price Index (California, 1972-73 to 1978-79); MCI: Medical Care Index (California, 1972-73 to 1978-79); MI = medically indigent; MN = medically needy; PA = public assistance

*Excludes renal dialysis program

care in 1978. Similarly, had the increases merely paralleled the overall Consumer Price Index increase of 8.2 percent per year, the total program cost would still have exceeded the actual payments in 1978 by more than $400 million. Indeed, as can be seen in Table 3, there would have been a lower figure in the Public Assistance program; however, this would have been more than offset by increases in the Medically Needy and the Medically Indigent categories.

Table 4 illustrates the changes in the number and composition of eligible beneficiaries in the three major components of the Medi-Cal program and estimates what the total program cost would have been, based on actual per eligible expenditures, if the breakdown by category in 1978 had remained about the same as in 1973 (86.5 percent, Public Assistance; 6.2 percent, Medically Needy, and 7.3 percent, Medically Indigent). The final column of Table 4 indicates the total estimated annual payments if the eligibility distribution had remained static, compared with actual expenditures in the preceding column. The reader will note that expenditures would have been almost $400 million lower if the overall program growth had been uniform among the various types of beneficiaries, rather than disproportionately higher for the more expensive Medically Needy and Medically Indigent components.

Finally, Table 5 provides an estimate of what the five-year increase in the cost of the Medi-Cal

program would have been if both the number and composition of persons eligible had remained the same as in 1973. This estimation, therefore, removes the effect of both the aggregate increase in the number of eligibles and the more important factor of disproportionately sharp increases in the number of high-cost eligibles—that is, Medically Needy and Medically Indigent eligibles. Having factored out these changes, the resulting hypothetical increase in program costs reflects exclusively price and utilization change.

Using this model, the total increase over the five years would have amounted to a total of 34.8 percent—or slightly less than 6.2 percent per year. This rate of increase compares very favorably not only with the general increase in medical care prices noted earlier, but also with the rate of increase in the overall Consumer Price Index which was estimated at 8.2 percent per year during the period.

Based on all of the foregoing calculations, it should be concluded that the increase in the cost of the Medi-Cal program has not been excessive. Rather, it has been extremely moderate compared with other factors in California's economy. Indeed, the primary reasons for continuing increases have been changes in eligibility, with the considerable expansion of programs in which the cost per eligible is necessarily high. This change in program configuration, coupled with the aggregate expansion in the number of persons eligible for Medi-Cal benefits, has resulted in a program which has understandably shown a *bottom line* growth of considerable magnitude. This growth should not be attributed to those who provide medical services, however, but rather to implementation of a social philosophy which has determined that both *more* and *different* persons should be eligible for benefits under a continually enriched program. Whether such persons should or should not be eligible for benefits is not the issue. The issue is whether there have in fact been "runaway costs" under the program, as alleged by the Department of Health Services, and whether a change in its configuration can result in substantive savings of state funds.

The authors do not feel that any available data suggest that changes in the method of delivering services will deal with the basic issue of cost, which derives from eligibility and scope of benefits. Rather, public policy makers must determine which of the following alternatives the taxpayers prefer:

- Continue funding the program with benefits

TABLE 4.—*1978 Medi-Cal Payments,* Actual and Hypothetical (Based on Eligibility Breakdown if Unchanged Since 1973)*

	1973			1978			
						Annual Payments (000)	
Program	*Number Eligible*	*Percent of Eligibles*	*Total Annual Payments (000)*	*Number Eligible*	*Percent Eligible*	*Actual*	*If Percent Were Same as 1973*
PA	1,794,248	86.5	$ 809,349	2,037,609	73.3	$1,504,266	$1,774,702
MN	127,957	6.2	322,376	331,361	11.9	740,829	385,230
MI	151,168	7.3	166,430	410,179	14.8	601,558	297,524
TOTAL ..	2,073,373	100.0	$1,298,155	2,779,149	100.0	$2,846,653	$2,457,456

MI = medically indigent; MN = medically needy; PA = public assistance

*Excludes renal dialysis program

TABLE 5.—*Percent Change in Total Fee-for-Service Payments Under Three Major Medi-Cal Programs IF There Had Been No Change in Eligibility Between 1973 and 1978*

Program	*Number of Eligibles, 1973*	*Average Monthly Payments, 1973*	*Total Annual Payments, 1973 (000)*	*Average Monthly Payments, 1978*	*Total 1978 Annual Payments IF Number of Eligibles Were as in 1973 (000)*
PA	1,794,248	$ 37.59	$ 809,349	$ 61.52	$1,324,586
MN	127,957	209.95	322,376	186.31	286,076
MI	151,168	91.75	166,430	122.21	221,691
TOTAL	2,073,373	$ 54.65	$1,359,825*	$ 73.65	$1,832,353
Increase 1973-78 ...	..	..	..	34.8%	

*Total also includes county hospital and state hospital payments, which are not separable by specific program.

as currently structured and, allowing for possible further expansion, accept the fact that this is a necessarily expensive but nevertheless an important social program;

- Freeze the composition of the program and its benefits, allowing expansion only to the extent that additional Californians qualify for benefits under current eligibility requirements;
- Curtail eligibility standards or program benefits or both to meet federally acceptable levels that existed at some point earlier in Medi-Cal's 14-year history; or
- Institute a method of graded "participatory responsibility" by recipients so that they, as well as other members of society, become watchdogs of public monies.

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Injury From Ingestion of Corrosive Agents

THE EXPERIENCE of the first 50 years of this century indicated that corrosive injuries of the upper gastrointestinal tract were largely confined to the esophageal membrane. This is due to the fact that most ingested corrosive agents were strong alkalis, prepared in the dry pellet, pill or flake form. When taken by mouth, these anhydrous materials tended to adhere to the surface of the esophageal membrane, go into solution with the addition of saliva, and produce local necrosis which later heals to yield a segmental stricture. . . . In the mid-1960's the innovative chemical industry began to formulate strong corrosive agents in a liquid form. For the first time, the consumer could run down to his favorite supermarket and purchase household and plumbing cleaners, air fresheners, and so on, containing liquid alkalis, liquid phenols and liquid acid preparations. . . . These liquid agents pass quickly through the esophagus into the stomach, where maximum corrosive injury takes place. . . . While we must consider the potential of esophageal injury, the stomach and, to a lesser degree, the duodenum deserve increasing emphasis and our best diagnostic efforts.

—LOUIS W. WELSH, MD, *Jenkintown, Pennsylvania*

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Information

Inability of an Iodination Method to Destroy Completely *Giardia* Cysts in Cold Water

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In 1975 Kahn and Visscher reported in this journal[1] that they had acquired giardiasis after drinking water from a partially frozen stream on the Long Valley trail to Mount San Jacinto, California; as a result they became interested in water disinfection. In the same article, they proposed a simple method of iodination to be used by travelers and hikers for the disinfection of small quantities of water in the wilderness.

Kahn and Visscher pointed out that a water disinfectant must be able to kill the hardiest stage of each group of organisms, especially the cyst form of amoebae. The method of disinfection that they recommended, however, had not been tested against *Giardia* cysts; therefore, the many recent outbreaks of waterborne giardiasis that have been reported[2-6] necessitate such testing.

Material and Methods

In the past, evaluating the efficacy of methods of disinfection against *Giardia* cysts was hampered by the lack of a sensitive technique for determining *Giardia* cyst viability. Recently, a method of inducing *Giardia* excystation in vitro was developed,[7] and has been used as the criterion of cyst viability to test Kahn and Visscher's method of water disinfection.

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The *Giardia* cysts used in these experiments were purified and concentrated[8] from a single human fecal specimen and stored in deionized water at 3°C. The cyst concentration was determined by counts using a hemacytometer.

The two water qualities tested were designated as "clear" and "cloudy." To simulate clear water in our laboratory, deionized water was obtained from a water conditioning system (Continental Water Conditioning Corporation, El Paso, Texas). This system delivered water that was determined to have a pH of 7.1 and to be iodine demand-free. The cloudy water (water that is not clear because of bacteria, nitrogenous compounds and so forth) was obtained from the Willamette River at Portland. This water was determined to have a pH of 7.2, a most probable number[9] of coliform bacteria of 23 per dl, and no detectable levels of iodine or chlorine. Iodine and chlorine residuals were determined by titration using a Wallace and Tiernan amperometric titrator.

The stock solution of saturated iodine was prepared as directed by Kahn and Visscher,[1] and allowed to stand at 20°C for at least 24 hours before use.

The experimental procedure was as follows: Two 1-liter glass beakers were filled with 1,000 ml of the water to be tested, allowed to equilibrate to, and then maintained at, 3° and 20°C. The recommended[1] quantity of saturated iodine stock solution was added to the test beakers according to the water quality and temperature, and the solutions were mixed with a mechanical paddle stirrer. Initial iodine levels were determined, and the cyst suspension was added to each beaker to a final concentration of approximately 1,000 cysts per ml. After 15, 30 and 40 minutes of contact time, two 50-ml samples of each solution were removed. The iodine residual and final pH were determined in one, and 3 ml of a 0.6 percent solution of sodium thiosulfate were added to the other specimen to stop the action of the iodine. The solutions containing thiosulfate were then centrifuged at 600 g for five minutes and the resulting cyst pellet was exposed to the excystation procedure.[7] Cysts suspended in clear and cloudy water without disinfectants were used as controls, and were otherwise treated the same as the disinfectant solutions. Control excystation ranged from 32 percent to 50 percent depending on the day that the experiments were done. The experimental protocol involved simultaneously

conducting the two disinfection treatments and the appropriate controls at each water quality and temperature. Data from controls containing sodium thiosulfate, which did not affect cyst viability, are not included in this report.

The results are expressed as percent cyst mortality and were calculated in the following manner: The percent excystation after exposure to the disinfectant was expressed relative to control excystation, which was arbitrarily designated as 100 percent. These numbers, subtracted from 100 percent,[10] represent cyst mortality.

Results

The results of representative experiments are presented in Table 1. Clearly, they show that even after 40 minutes of contact time, complete destruction of *Giardia* cysts did not occur at 3°C, regardless of the water quality. The data do suggest, however, that if the contact time or the iodine residual were increased sufficiently, the efficacy of this method for cold water disinfection could prove satisfactory. The increased cysticidal activity of iodine in cold, clear water above that in cold, cloudy water can be attributed to the higher iodine residual. This higher residual is due, for the most part, to a lack of iodine demand by the clear water.

At 20°C, Kahn and Visscher's method of disinfection destroyed more than 99.8 percent of the *Giardia* cysts in both clear and cloudy water after 15 minutes, even though the cloudy water had a low iodine residual.

It should be noted that several times during the course of these experiments we obtained lower iodine residuals than those predicted by Kahn and Visscher. Part of this discrepancy may be attributed to the cyst demand for iodine, but much of it probably resulted from variation in the concentration of the iodine in the "saturated" iodine stock solution. Even though the water used in part of these experiments was demand-free and the measurement of the stock iodine solution was done carefully, iodine residuals were occasionally in excess of 1 part per million below those predicted. Such a reduced iodine concentration, particularly when coupled with a decrease in temperature or an increase in the iodine demand of the water, or both, could be hazardous. The ineffectiveness of this and other small-quantity water disinfection methods[11] in the combined presence of low water temperature and increased iodine demand cannot be overemphasized as evidence is available which indicates that survival of *Giardia* cysts is prolonged in cold water.[8] Furthermore, no water in the wilderness, regardless of its apparent clarity, can be more iodine demand-free than the clear water used in this study. Thus, while 95.9 percent of the cysts in cold, clear water were destroyed, a lower level of destruction can be expected in actual use.

The data presented here do not permit the formulation of a modified method of using a saturated iodine solution that will ensure *Giardia* cyst destruction in cold water. It should be pointed out, however, that two other small-quantity water disinfection methods, when tested using the excystation procedure discussed above, have effectively destroyed *Giardia* cysts at 3°C.[11] Furthermore, it has been shown that bringing water to the boiling point destroys *Giardia* cysts instantaneously,[8] so that a method of killing these organisms is available, even when chemical water treatment methods are not.

TABLE 1.—*Effect of Saturated Iodine Treatment on* Giardia *Cysts in Clear and Cloudy Water*

	Clear Water							
	3°C (26 ml of stock iodine solution)				20°C (13 ml of stock iodine solution)			
	Control	*15 min.*	*30 min.*	*40 min.*	*Control*	*15 min.*	*30 min.*	*40 min.*
RI*	0	6.87	6.87	6.87	0	3.29	3.29	3.29
Percent cyst mortality	0	56.5	93.3	95.9	0	>99.8	>99.8	>99.8
Final pH	7.1 (range, 7.0-7.1)				7.1 (range, 7.0-7.1)			
	Cloudy Water							
	3°C (26 ml of stock iodine solution)				20°C (26 ml of stock iodine solution)			
	Control	*15 min.*	*30 min.*	*40 min.*	*Control*	*15 min.*	*30 min.*	*40 min.*
RI	0	4.58	4.58	4.58	0	3.01	3.01	3.01
Percent cyst mortality	0	37.2	57.5	81.5	0	>99.8	>99.8	>99.8
Final pH	7.3 (range, 7.0-7.3)				7.3 (range, 7.0-7.3)			

*Residual iodine in parts per million.

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Information

Pack Palsy in Backpackers

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UPPER EXTREMITY NUMBNESS, weakness and atrophy associated with the use of a heavy backpack have been reported in military personnel[1-4] and termed pack palsy or rucksack paralysis. Compression of the upper trunk of the brachial plexus[1,2] or peripheral nerve supply to the shoulder girdle[3,4] by backpack straps is implicated as the causative mechanism.

In several of the cases factors were present which could predispose a person to this type of injury. These included nutritional deficiency,[1] structural abnormalities in the neck and shoulder[2] and previous partially denervated shoulder musculature.[4] The presence of these predisposing factors and the occasional occurrence of an upper extremity neuropathy in military personnel without backpack trauma led Weinstein[5] to state that "pack palsy does not exist as a primary entity." A neuropathic condition similar to that seen following routine immunizations is cited as a probable mechanism for these cases.[5] However, a sufficient number of cases have been reported without predisposing factors or recent immunizations to suggest that pack palsy does exist.[2-4]

Despite the many case reports from the military, communications regarding pack palsy in civilians are rare. Compression of the brachial plexus by a backpack has been reported in four adolescent Boy Scouts,[6] and in one man.[7] Underdeveloped musculature has been suggested as a predisposing factor in the cases in adolescents.[2]

In view of the increasing popularity of backpacking, civilian physicians should be reminded of the occurrence of pack palsy. The present communication documents our experience with three civilian men with weakness, atrophy of shoulder muscles, or both, associated with backpacking.

Reports of Cases

CASE 1. A 23-year-old, right-handed man complained of nonprogressive muscle wasting and weakness of the right shoulder of a year's duration.

For three years the patient had been backpacking frequently using an internal frame pack and waistband, and carrying a 30-kg load. After several hours of climbing or hiking he would experience right shoulder pain, numbness of the entire right arm and right shoulder girdle weakness. Removal of the backpack for several minutes led to prompt relief of symptoms, but they would return if hiking or climbing was resumed. Between trips the patient was asymptomatic.

A year before evaluation the patient experienced similar symptoms during a backpacking trip. However, the weakness of the shoulder girdle did not respond to pack removal, although pain and numbness disappeared. Following this trip the patient noted persistent weakness of the right shoulder girdle and atrophy of shoulder musculature.

Despite the persistent weakness and atrophy the patient made another backpacking trip a month later. During this trip he carried more weight on the left side of the pack because of

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weakness in his right arm. He felt bilateral arm pain, numbness, and shoulder girdle weakness (right greater than left). Pack removal relieved the pain, numbness and left arm weakness. Following this trip the patient noted increased right shoulder weakness and wasting and some left shoulder wasting without weakness. No progression or improvement of symptoms occurred up to the date of examination.

Past medical history disclosed no neck or arm trauma, immunizations, viral illness or diabetes before onset of symptoms.

On examination the patient was noted to be 1.78 meters (5 ft 10 in) tall and weighed 61.2 kg (134.9 pounds). Blood pressure was 120/70 mm of mercury in both arms and pulses were equal. A general physical examination showed no abnormalities.

Figure 1.—Four views of patient 1 showing bilateral scapular winging and spinatus atrophy, which is greater on the right side.

Figure 2.—Four views of patient 1 showing position of the pack straps relative to the neck and shoulder, and right trapezius atrophy (lower photogaphs). Note that the backpack straps cross potential compression sites for accessory, long thoracic and suprascapular nerves as well as the upper trunk of the brachial plexus.

A neurological examination showed mental status, cranial nerve, coordination, reflex and detailed sensory measurements to be within normal limits. On motor testing, tone was normal. There was pronounced atrophy (Figures 1 and 2) of the right trapezius, supraspinatus and infraspinatus. Milder atrophy was noted in the left spinati and bilateral scapular winging was present. Weakness of both serratus anterior muscles, the right trapezius and right spinati was present.

X-ray studies of the cervical spine and chest, as well as a complete myelogram showed no abnormalities. Results of laboratory evaluation were unremarkable.

Electromyographic abnormalities were limited to the right trapezius, serratus anterior, supraspinatus and infraspinatus. In these muscles decreased insertional activity was seen in association with fibrillations and positive sharp wave potentials. During voluntary contraction the interference pattern was reduced and motor units were polyphasic and of increased amplitude and duration. The impression was partial denervation of the involved muscles.

Nerve conduction studies from Erb point to bilateral trapezii and spinati showed slowed conduction to all three muscles on the right and to the left infraspinatus. Evoked potential amplitudes on the left were six to seven times greater than on the right.

Case 2. A 26-year-old, right-handed man complained of left shoulder wasting and weakness of five months' duration.

Six months before evaluation the patient contracted hepatitis B. During his illness he complained of generalized arthralgias, myalgias and a subjective feeling of weakness in both shoulders.

A month later the patient went on a backpacking trip while recovering from his hepatitis. He used an external frame pack and carried a load of 20 kg. Following the backpacking trip he noted painless left shoulder weakness and subsequent atrophy of the left spinati. The weakness and atrophy were nonprogressive after initial discovery, and strength was returning by the time of evaluation.

Past medical history disclosed no recent viral illnesses other than the hepatitis B. Gamma glob-

ulin had been administered six months before the onset of weakness, at the time of known exposure to hepatitis. There was no history of neck or arm trauma or diabetes before onset of arm symptoms.

On examination the patient was found to be 1.75 meters (5 ft 9 in) tall and weighed 72.6 kg (160 pounds). Blood pressure was 110/80 mm of mercury in both arms and pulses were equal. Results of a general physical examination were normal.

Neurologic examination showed mental status, cranial nerve, coordination, reflex and detailed sensory measurements to be within normal limits. On motor testing tone was normal. There was atrophy of the left supraspinatus and infraspinatus. Muscle strength was normal except for weakness of the left spinati.

X-ray studies of the cervical spine, shoulder and chest as well as recent routine laboratory tests showed no abnormalities.

Electromyographic abnormalities were limited to the left supraspinatus and infraspinatus. In these muscles slightly increased insertional activity was seen in association with fibrillations and positive sharp wave potentials. During voluntary contraction the interference pattern was reduced but motor units were otherwise normal. The impression was partial denervation of the left spinati.

Follow-up evaluation was carried out ten months after weakness began. Motor strength in the left spinati was essentially normal while some atrophy remained.

Follow-up electromyography of the left spinati disclosed normal insertional activity. The left supraspinatus showed occasional fibrillations and positive sharp wave potentials, while the left infraspinatus showed no abnormal rest activity. In both muscles motor unit potentials of normal amplitude, duration and configuration were seen with a normal interference pattern during contraction.

Nerve conduction studies from Erb point to the shoulder musculature showed normal latencies ten months after injury.

Case 3. A 29-year-old, right-handed man complained of winging of the left scapula noted 72 hours before examination.

Nine days before evaluation the patient went on a backpacking trip for several days. He used an external frame pack and carried an 18-kg load. He noted some mild discomfort from the straps of the pack but did not feel arm pain or numbness. On one night of the trip, his air mattress partially collapsed and his sleeping position may have been abnormal that night. Forty-eight hours after the trip he realized his left scapula was winging. However, the winging was nonprogressive during the next 72 hours, when he was examined.

Past medical history disclosed no recent immunizations, viral illnesses, history of diabetes, or neck and arm trauma before the camping trip.

On examination the patient was noted to be 1.83 meters (6 ft) tall and weighed 81.6 kg (179.9 pounds). Results of a general physical examination were unremarkable.

On neurological examination, mental status, cranial nerve, coordination, reflex and detailed sensory measurements were within normal limits. On motor testing, tone was normal. The only abnormality noted was mild left scapular winging.

The patient was reevaluated 19 days after the onset of scapular winging. At that time no winging was noted.

Electromyographic abnormalities were limited to the left serratus anterior. Normal insertional activity was noted as was normal rest activity. During voluntary contraction a reduced interference pattern was observed but motor units were otherwise normal. The impression was neurapraxia or partial denervation of the long thoracic nerve.

Discussion

Despite the fact that most pack palsy cases in the literature are thought to be due to brachial plexus compression,[1,2,6,7] peripheral nerve injury appears to be the mechanism in the three cases reported above. In case 1 the patient had accessory nerve involvement (not part of brachial plexus), as well as involvement of only muscles innervated by the suprascapular and long thoracic nerves. This is in contrast to patients with plexus compression, in which there is more diffuse C5-C6 involvement and almost invariable deltoid involvement.[2] Cases of compression of the accessory[4] and long thoracic[3,4] nerve by backpacks have been reported. Suprascapular nerve compression at the scapular notch has been reported from other causes.[8] In case 2 (suprascapular nerve) and case 3 (long thoracic nerve) the patients had only single nerve involvement. Their conditions are also dissimilar to those involving plexus compression.

Case 1 probably represents pure pack palsy as no predisposing factors could be documented. Of

interest, however, is the fact that the patient carried a heavy load compared with his own body weight (49 percent) using an internal frame pack. This exceeds the load recommended by many outfitters (personal communications).

Predisposing factors may have been present in the remaining cases. The hepatitis B in patient 2 may have rendered his peripheral nerves more sensitive to injury, because the load he carried appeared to be within safe limits. Patient 3 may have had an abnormal sleep posture as a predisposing factor in long thoracic nerve injury because his load was also within safe limits.

Regardless of the site of compression, the prognosis for complete recovery from pack palsy within three months after injury approaches 87 percent.[7] Recovery in patients 2 and 3 was good and followed the expected course for this entity although it was slow in patient 2. In the case of patient 1, however, no improvement was noted in his condition a year after onset. In all probability repeated trauma to affected nerves by continued backpacking adversely affected his prognosis.

Treatment of pack palsy consists primarily of removing the source of trauma by avoidance of further backpacking during recovery. Daube[2] suggests that the use of a pack should be discontinued until at least a month after complete recovery occurs. During the recovery phase further trauma of any type to the brachial plexus or to nerves to the shoulder girdle should be avoided, as should heavy lifting with an outstretched arm. A sling may be useful when trapezius or deltoid weakness allows shoulder separation. Heavy therapeutic exercise programs will probably be unnecessary and may be harmful.[9] Most patients with pack palsy will be able to do sufficient mild exercise during their normal activities to strengthen upper extremities as recovery occurs.

Civilian as well as military physicians should consider pack palsy as a possible cause or contributing factor in patients presenting with unexplained weakness and wasting of the arm and shoulder girdle. Appropriate history-taking will help to establish the possibility of this diagnosis, and clinical and electrodiagnostic testing will help to localize the process to the upper trunk of the brachial plexus or to the nerves to the shoulder musculature. While other disease processes must still be considered and ruled out, the proper diagnosis of pack palsy permits appropriate treatment for this cause of arm wasting and weakness.

Summary

Pack palsy, secondary to compression of the upper trunk of the brachial plexus or peripheral nerve supply to the shoulder girdle by backpack straps, has been thought to be essentially a military medical problem. However, this report presents three cases of pack palsy in civilian backpackers in which peripheral nerve compression appears to be the cause. Recovery from pack palsy is usually good, although prolonged dysfunction may occur if the condition is not recognized, thus permitting repeated trauma to neural tissue to occur. Treatment primarily involves removal of the source of the trauma.

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in memoriam

California Medical Association

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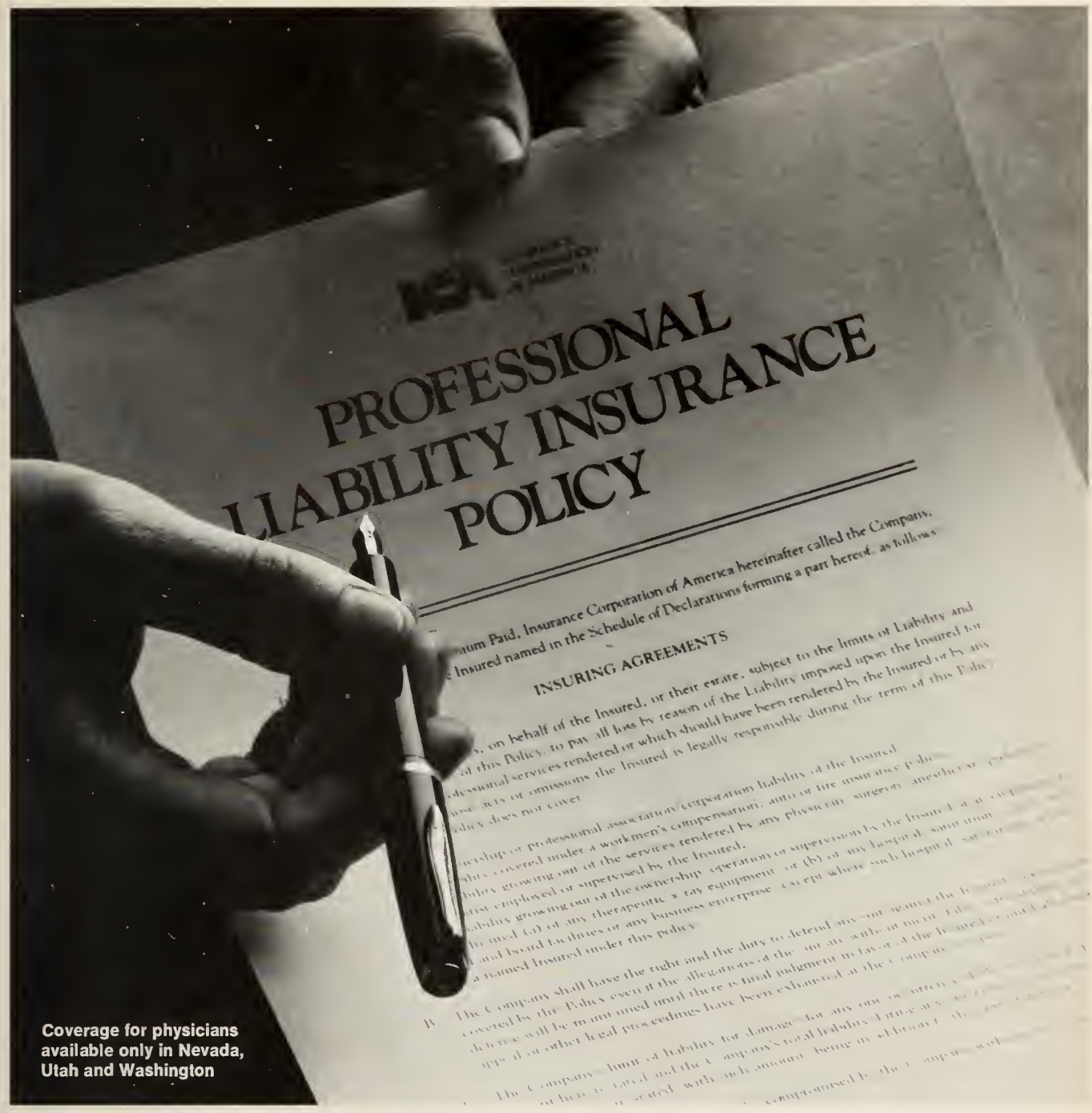

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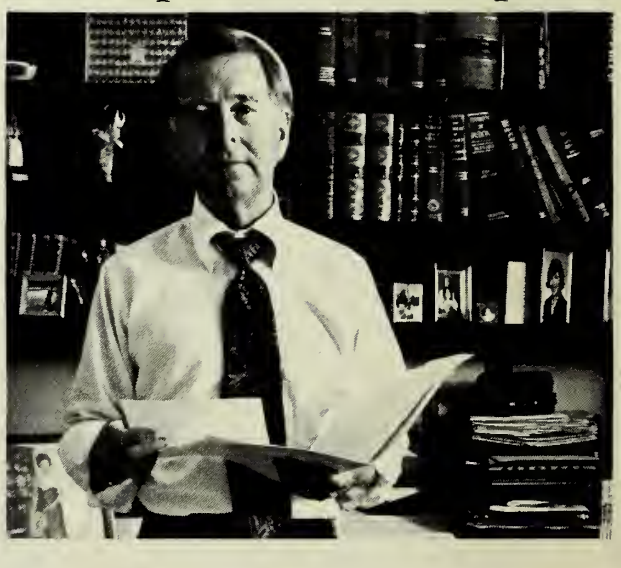

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANNUAL REVIEW OF NEUROSCIENCE—Volume 3, 1980—Editor: W. Maxwell Cowan, Washington University School of Medicine; Associate Editors; Zach W. Hall, University of California, San Francisco; and Eric R. Kandel, College of Physicians and Surgeons of Columbia University. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, CA (94306), 1980. 428 pages, $17.00.

BEHAVIORAL SCIENCE IN FAMILY PRACTICE—Editors: Gerald M. Rosen, PhD, Clinical Assistant Professor, Department of Family Medicine, University of Washington; John P. Geyman, MD, Professor and Chairman, Department of Family Medicine, University of Washington, and Richard H. Layton, MD, Clinical Professor in Family Medicine, Director, Providence Family Medical Center, Seattle. Appleton-Century-Crofts, 292 Madison Avenue, New York City (10017), 1980. 304 pages, $19.50.

CLINICAL ASPECTS OF MALPRACTICE—Robert S. Pollack, MD, honorary and consulting surgeon, Presbyterian Hospital, San Francisco; attending surgeon at Children's and St. Francis Hospitals, San Francisco; chief consulting surgeon, US Public Health Service Hospital, San Francisco, and Veterans Administration Medical Centers, Martinez and Livermore; and clinical professor of surgery and oncology, University of the Pacific School of Dentistry, San Francisco. Medical Economics Books, Box 157, Florence, KY (41042), 1980. 210 pages, $18.95 plus $1 handling charge.

CURRENT PEDIATRIC DIAGNOSIS & TREATMENT—Sixth Edition—C. Henry Kempe, MD, Professor of Pediatrics and Microbiology; Henry K. Silver, MD, Professor of Pediatrics, and Donough O'Brien, MD, FRCP, Professor of Pediatrics, University of Colorado School of Medicine, Denver; and associate authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1980. 1122 pages, $20.00.

DIRECTING HEALTH-CARE VOLUNTEERS—Nancy Kieffer. Medical Economics Books, Box 157, Florence, KY (41042), 1980. 245 pages, $12.95.

ENGRAMMES OF THE UNIVERSE—Extra-Cerebral Memory, Reincarnation, Demonic Possession—J. M. Sanchez-Perez, MD. Exposition Press, Inc., 900 South Oyster Bay Road, Hicksville, NY (11801), 1980. 141 pages, $8.50.

GENERAL OPHTHALMOLOGY—Ninth Edition—Daniel Vaughan, MD, Clinical Professor of Ophthalmology, University of California, San Francisco; and Taylor Asbury, MD, Professor of Ophthalmology, Director, Department of Ophthalmology, College of Medicine, University of Cincinnati; illustrated by Laurel V. Schaubert. Lange Medical Publishers, Drawer L, Los Altos, CA (94022), 1980. 410 pages, $15.00.

A GUIDE TO I.V. ADMIXTURE COMPATIBILITY—Third Edition—By arrangement with New England Deaconess Hospital, Boston. Medical Economics Books, Box 157, Florence, KY (41042), 1980. 68 pages, $5.95, plus $1 handling charge (softcover).

NUCLEAR MEDICINE REVIEW SYLLABUS—Senior Editor: Peter T. Kirchner, Chicago; Associate Editors: William C. Eckelman, Washington, DC, Stanley J. Goldsmith, New York, Thomas G. Mitchell, Baltimore, Richard C. Reba, Washington, DC, Barry A. Seigel, St. Louis, H. William Strauss, Boston, and Richard L. Witcofski, Winston-Salem, NC. The Society of Nuclear Medicine, Inc., 475 Park Avenue South, New York City (10016), 1980. 619 pages, $30.00.

THE PILATES METHOD OF PHYSICAL AND MENTAL CONDITIONING—Philip Friedman and Gail Eisen. Doubleday & Company, Inc., 245 Park Avenue, New York, NY (10017), 1980. 191 pages, $12.95.

PRESIDENTIAL COURAGE—John B. Moses, MD, and Wilbur Cross. W. W. Norton & Company, Inc., Publishers, 500 Fifth Avenue, New York City (10036), 1980. 249 pages, $11.95.

RISK, COMMUNICATION, AND DECISION MAKING IN GENETIC COUNSELING—Part C of ANNUAL REVIEW OF BIRTH DEFECTS, 1978—Editors: Charles J. Epstein, MD, Departments of Pediatrics, and Biochemistry and Biophysics, University of California, San Francisco; Cynthia J. R. Curry, MD, Genetics Unit, Valley Children's Hospital, Fresno, California; Seymour Packman, MD, Department of Pediatrics, University of California, San Francisco; Sanford Sherman, MD, Children's Hospital Center, Oakland, California; Bryan D. Hall, MD, Department of Pediatrics, University of California, San Francisco; Associate Editor: Sue Conde Greene, The National Foundation; Assistant Editor: Marcia C. MacDonald, The National Foundation-March of Dimes. Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1979. 376 pages, $36.00.

SENSORY FUNCTIONS OF THE SKIN OF HUMANS—Proceedings of the Second International Symposium on Skin Senses, Tallahassee, Florida, June 5-7, 1978—Edited by Dan R. Kenshalo, Florida State University, Tallahassee. Plenum Press, 227 West 17th St., New York (10011), 1979. 439 pages, $39.50.

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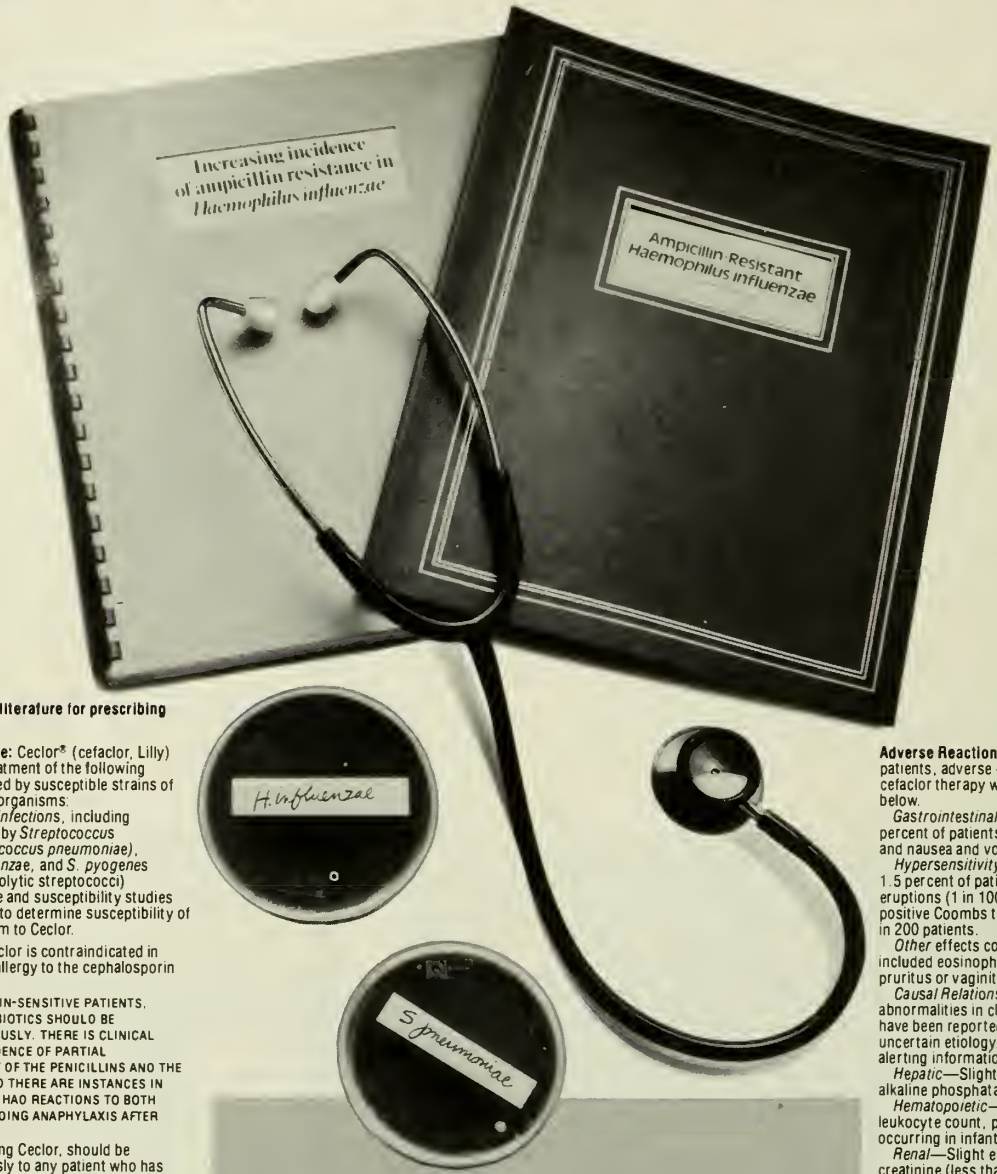
An added complication... in the treatment of bacterial bronchitis*



Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE).

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: In clinical studies in 1493 patients, adverse effects considered related to cefaclor therapy were uncommon and are listed below.

Gastrointestinal symptoms occurred in about 2.5 percent of patients and included diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions were reported in about 1.5 percent of patients and included morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occurred in less than 1 in 200 patients.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory tests results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [070379R]

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

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*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[8]

Note: Ceclor® (cefaclor) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

References

1. Antimicrob. Agents Chemother., *8*:91, 1975.
2. Antimicrob. Agents Chemother., *11*:470, 1977.
3. Antimicrob. Agents Chemother., *13*:584, 1978.
4. Antimicrob. Agents Chemother., *12*:490, 1977.
5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II: 880. Washington, D.C.: American Society for Microbiology, 1978.
6. Antimicrob. Agents Chemother., *13*:861, 1978.
7. Data on file, Eli Lilly and Company.
8. Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr., and J.E. Bennett), p. 487. New York: John Wiley & Sons, 1979.

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

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ANESTHESIOLOGY

October 3-5—**Anesthesia Specialties.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Del Monte Hyatt, Monterey. Friday-Sunday. 10½ hrs. $90, AEF member; $165, nonmember. Contact: Walter H. Comer, MD, AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

October 26-28—**Anesthesia and Cardiopulmonary Disease.** Calif. Society of Anesthesiologists at Del Monte Hyatt, Monterey. Sunday-Tuesday. 11 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

November 8-9—**American Society of Anesthesiologists—Refresher Course.** Hilton, San Francisco. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

December 12-14—**Anesthesia: Before and After.** Tucson Hospitals Medical Education Program at Canyon Hotel, Palm Springs. Friday-Sunday. $150. Contact: James P. Angiulo, MD, Kino Community Hosp., 2800 E. Ajo Way, Tucson, AZ 85713.

CANCER

September 6-7—**2nd Annual Preventive Oncology: Nutrition and Cancer.** UCSF and No. Calif. Cancer Program. Saturday-Sunday. $130. Contact: UCSF, Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

October 9-11—**American Cancer Society.** Hilton, Los Angeles. Thursday-Saturday. Contact: N. G. Bolliglieri, MD, ACS, 777 Third Ave., New York 10017.

October 24-26—**Enzymes and Related Proteins in the Diagnosis and Prognosis of Neoplastic Diseases.** UCSD at Vacation Village, San Diego. Friday-Sunday.

October 27-29—**4th Annual Cancer Symposium.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. 22 hrs. $300. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

Noember 6-8—**Current Concepts in Cancer Diagnosis.** UCLA. Thursday-Saturday.

November 7-8—**Cancer Prevention and Screening.** Claire Zellerbach Saroni Tumor Institute of Mt. Zion Hospital and Medical Center at Holiday Inn on Union Square, San Francisco. Friday-Saturday. 10 hrs. $125 before September 15; $150 thereafter. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

EMERGENCY MEDICINE

June 17—**Death in the Emergency Department.** St. John's Hospital and Assn. for Emergency Physicians for Ventura and Santa Barbara Counties at St. John's Hospital, Oxnard. Tuesday; 8:00 p.m. 1½ hrs CMA and ACEP. Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

June 18-20—**Radiology in the Emergency Room Department.** UCSF at Fairmont Hotel. Wednesday-Friday.

June 19—**Plastic Surgery in the Emergency Department.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

June 20-22—**Recognition and Management of Poisonings and Toxicological Emergencies.** UCSF, S.F. Bay Area Reg. Poison Control Ctr., Am. Assn. of Poison Control Ctrs. and Am. Academy of Clinical Toxicology at Jack Tar Hotel, San Francisco. Friday-Sunday. 17 hrs. Contact: Dr. Kenneth W. Lem, UCSF, San Francisco 94143. (415) 666-4194.

June 23-27—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

June 27-28—**Ophthalmology and ENT for Emergency Room Physicians.** PMC. Friday-Saturday. 12 hrs.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717. (714) 833-5414, Fee and Information office or (714) 833-5526, 5542, Continuing Education in Health Sciences.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

July 14-18—**Medical Management of EMS Systems.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs.

July 21-25—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

July 25-27—**Advanced Cardiac Life Support Provider, Recertification and Instructor Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, Education Dept., 2310 Mason St., San Francisco 94133. (415) 956-5900.

August 11-15—**Postgraduate Institute for Emergency Physicians, Symposium I:** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

September 18—**Abdominal Trauma.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

October 3-4—**Postgraduate Institute on Emergency Medicine—5th Annual.** UCLA at Miramar-Hilton, Santa Monica. Friday-Saturday. 14 hrs. $170.

October 13-17—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

October 16—**Dermatology in the Emergency Department.** UCSD. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

October 20-31—**Intensive Review of Emergency Medicine.** USC. Two weeks.

November 20—**Clinical Pharmacology in the Emergency Department.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

December 8-12—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

MEDICINE

June 18—**The Diagnosis and Management of the Newborn With Cardiorespiratory Disease.** American Heart Assn., Greater Los Angeles Affiliate, at New Otani Hotel, Los Angeles. Wednesday. 6 hrs. $50, member; $60, nonmember. Contact: Mary Frances Flynn, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

June 20-21—**Medical Knowledge Self Assessment—Group C.** American College of Physicians and PMC at Hyatt Regency, San Francisco. Friday-Saturday. Contact: PMC.

June 21-22—**American Association for the Study of Headache.** Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: S. Diamond, MD, Exec. Sec., 5252 N. Western Ave., Chicago 60625.

June 27-29—**Hepatobiliary Disease in Clinical Practice.** American College of Physicians at Holiday Inn on Union Square, San Francisco. Friday-Sunday. 15 hrs. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

July 8-10—**Podiatric Dermatology.** STAN. Tuesday-Thursday. 17 hrs.

July 11-13—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Hyatt Regency, San Francisco. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

July 12-19—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 23 hrs. $290.

July 29-August 3—**5th Annual Postgraduate Course and Workshop in Medical Mycology-Dermatomycology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Tuesday-Sunday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 2—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

August 7-9—**Society for Pediatric Dermatology—5th Annual Meeting.** SPD and STAN at Doubletree Inn, Monterey. Thursday-Saturday. 15 hrs. $150, members; $200, nonmembers. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

August 8-9—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Saturday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

August 13—**Calcium Metabolism—Its Diagnosis and Management.** LLU. Wednesday. 4 hrs. $30.

August 14-16—**A Pan-Pacific Conference on Tuberculosis in the 80s.** Hawaii Thoracic Society, Am. Lung Assn. of Hawaii, Hawaii Dept. of Health and Univ. of Hawaii at Ala Moana Hotel, Honolulu. Thursday-Saturday. $35. Contact: Hawaii Thoracic Society, 245 N. Kukui St., Honolulu 96817.

August 15-17—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

August 15-20—**Neuropsychiatric Issues in the Law, Education and Medicine.** See Psychiatry, August 15-20.

September 5—**13th Annual Symposium on Kidney Disease—Endocrine and Metabolic Functions of the Kidney.** Kidney Foundation of Northern Calif. at Fairchild Auditorium, Stanford Univ. Sch. of Med., Stanford. Friday. 6 hrs. $45. Contact: William Arnopp, Exec. Dir., KFNC, 100 S. Ellsworth Ave., Ste. 305, San Mateo 94401. (415) 347-6646.

September 10—**Hematuria—An Approach to Diagnosis and Therapy.** LLU. Wednesday. 4 hrs. $30.

September 18-19—**Hypertension.** UCD at Sahara, Lake Tahoe. Thursday-Friday. 15 hrs.

September 25-26—**Annual Physicians' Symposium.** American Heart Assn., San Francisco Chapter, at San Franciscan Hotel, San Francisco. Thursday-Friday. Contact: Kari Olila, AHA, 421 Powell St., San Francisco 94102. (415) 433-2273.

September 25-28—**American Society of Ophthalmologic and Otolaryngologic Allergy—Annual Meeting.** Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: William King, MD, 1415 3rd St., Corpus Christi, TX 78404.

September 26-27—**American Society of Internal Medicine.** Islandia Hyatt, San Diego. Friday-Saturday. Contact: ASIM, 2550 M St. NW, Suite 620, Washington, DC 20037.

September 26-28—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Hyatt on Union Square, San Francisco. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

September 27—**Management of Chronic Lung Disease.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

October 1-December 17—**Cardiology.** UCLA. Wednesday evenings.

October 4-11—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

October 8—**Endocrine Review.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. Contact:

Janie Sternal, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

October 8—**Modern Therapy for Common Dermatologic Problems.** LLU. Wednesday. 4 hrs. $30.

October 10-12—**Chest Disease Symposium.** The Cypress Foundation and UCSF at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Robert S. Meyer, Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

Ocober 13-17—**An Advanced Course for Internists.** STAN. Monday-Friday. 25 hrs. $290.

October 18-25—**Cardiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $325.

October 23-28—**Pacific Dermatologic Association.** Palm Springs. Thursday-Tuesday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno, NV 89509. (702) 323-2461.

October 27-30—**Practical Electrocardiography Course for Primary Physicians.** Memorial Hospital Medical Center-UCI Center for Health Education at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: Center for Health Education. 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 1—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

November 5-8—**American Thyroid Association.** Holiday Inn at the Embarcadero, San Diego. Wednesday-Saturday. Contact: L. E. Braverman, MD, Univ. of MA Medical Ctr., Worcester, MA 01605.

November 12—**Peptic Ulcer—Its Diagnosis and Treatment in the 1980's.** LLU. Wednesday. 4 hrs. $30.

November 17-19—**International Symposium on Status Epilepticus.** UCLA at Miramar-Sheraton, Santa Monica. Monday-Wednesday. 20 hrs.

November 19-21—**Pediatric Cardiology.** USC at Palm Springs. Wednesday-Friday.

December 1-3—**Cardiovascular-Pulmonary Update for the Practicing Physician.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Monday-Wednesday. 19 hrs. $265. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

December 5—**Recognition and Management of Bleeding Disorders.** Children's Hospital Medical Center of Northern Calif. at Sir Francis Drake Hotel, San Francisco. Friday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

December 5-7—**Cardiac Rehabilitation.** International Medical Education Corp. at Wilshire Hyatt, Los Angeles. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

December 6-7—**Neurology for the Primary Care Physician.** UCLA. Saturday-Sunday.

December 10—**Collagen Disease—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $30.

OBSTETRICS AND GYNECOLOGY

June 16-18—**Nutritional Care of High-Risk Obstetrical Patients and High-Risk Infants.** STAN. Monday-Wednesday. 18 hrs. $20.

August 9-15—**Reproductive Endocrinology, Infertility and Contraception.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

August 23-28—**Practical Management of the Infertile Couple.** See Of Interest To All, August 23-28.

September 12-13—**Environmental Hazards in Pregnancy: A Clear and Present Danger.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 12 hrs.

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November 5-7—**Tomorrow: A Follow-Up on Perinatal Care.** UCSD at Bahia Hotel, San Diego. Wednesday-Friday. 20 hrs. $185. Contact: Ronald W. Coen, MD, UCSD Sch. of Med., C-019, La Jolla 92093. (714) 452-4424.

PEDIATRICS

June 16-18—**Nutritional Care of High-Risk Obstetrical Patients and High-Risk Infants.** See Obstetrics and Gynecology, June 16-18.

June 18—**The Diagnosis and Management of the Newborn With Cardiorespiratory Disease.** See Medicine, June 18.

August 2—**Pediatric Dermatology.** See Medicine, August 2.

September 18-20—**Pediatric Urology.** UCD at Holiday Inn, Napa Valley. Thursday-Saturday. 12 hrs.

October 3-4—**Pediatric Topics: Neonatology.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 10 hrs. $85.

October 25—**Hearing Impaired Child.** Peninsula Hospital, Burlingame. Saturday. Contact: Susan Norrell, c/o Radiology Dept., Peninsula Hosp., 1783 El Camino Real, Burlingame 94010. (415) 697-4061, ext. 479.

October 25-November 1—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center-UCI Center for Health Education and L.A. Pediatric Society at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 21 hrs. $200. Contact: Center for Health Education, MHMC, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 1—**Pediatric Dermatology Seminar.** See Medicine, November 1.

November 5-7—**Tomorrow: A Follow-Up on Perinatal Care.** See Obstetrics-Gynecology, November 5-7.

November 19-21—**Pediatric Cardiology.** See Medicine, November 19-21.

December 5-7—**Children and Their Skeletons: A Practical Approach.** UCD at Hyatt Del Monte, Monterey. Friday-Sunday.

PSYCHIATRY

June 21-22—**Intellect and Illness.** UCLA. Saturday-Sunday.

June 23-27—**Comparative Psychotherapies.** USC at Hilton, San Diego. Monday-Friday.

August 1-3—**Child Psychiatry.** UCD at Holiday Inn-on-the-Beach, Monterey. Friday-Sunday.

August 15-20—**Neuropsychiatric Issues in the Law, Education and Medicine.** So. Calif. Neuropsychiatric Institute and Am. Psychiatric Assn. at Mauna Kea Beach Hotel, Kamuela, Hawaii. Friday-Wednesday. 14 hrs. Contact: Gail Waldron, MD, SCNPI, 6794 La Jolla Blvd., La Jolla 92037. (714) 454-2102.

October 25—**Cognitive Prospectives in Psychiatry.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

RADIOLOGY AND PATHOLOGY

June 16-25—**Radiology of Bone and Joint Disease.** UCSD at Hotel del Coronado, Coronado (June 16-19) and Kauai Surf Resort Hotel, Kauai, Hawaii (June 23-25). 7 days. 29 hrs. $500 (or $300 for first part; $200, second part).

June 18-20—**Radiology in the Emergency Room Department.** See Emergency Medicine, June 18-20.

June 22-27—**Pathology of the Lung.** UCSD. One week. 50 hrs. $450.

July 25-27—**Ultrasound Seminar.** American College of Radiology at San Francisco. Friday-Sunday. 15 hrs. $275. Contact: ACR, 20 N. Wacker Dr., Chicago 60606.

August 9-16—**Radiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

September 27-October 4—**Diagnostic Radiology.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

October 10-12—**Society of Nuclear Medicine—5th Annual Western Regional Meeting.** Airport Marriott, Los Angeles. Friday-Sunday. Contact: SNM, P.O. Box 40279, San Francisco 94140. (415) 647-5909.

October 24-26—**Advances in Immunopathology.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Friday-Sunday. 17 hrs. $120. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

June 19-20—**Office Orthopedics.** USC. Thursday-Friday.

June 19-21—**Highlights of Ophthalmology.** PMC at Hyatt Regency, San Francisco. Thursday-Saturday. $225.

July 9—**The Management of Acute Trauma.** LLU. Wednesday. 4 hrs. $30.

July 12-19—**Cardiovascular Medicine and Surgery: An Advanced Course.** See Medicine, July 12-19.

July 28-30—**Primary Care of Hand Injuries and Workshop on Hand Splints and Dressings.** American Society for Surgery of the Hand at Doubletree Inn, Monterey. Monday-Wednesday. 16 hrs. $250. Contact: Am. Soc. for Surgery of the Hand, 2600 S. Parker Rd., Ste. 132, Aurora, CO 80014. (303) 755-4588.

September 2-5—**IV International Symposium on Facial Nerve Surgery.** Ear Research Institute, Los Angeles. Tuesday-Friday. Contact: Facial Nerve Symposium, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

September 10—**Hematuria—An Approach to Diagnosis and Therapy.** LLU. Wednesday. 4 hrs. $30.

September 13-20—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

September 18-20—**Pediatric Urology.** See Pediatrics, September 18-20.

September 19-20—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

September 25-28—**Cost Effective Urological Diagnosis and Treatment.** Western Section, Am. Urological Assn. and AUA at Marriott's Rancho Las Palmas Resort, Palm Springs. Thursday-Sunday. Contact: Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

September 26-27—**Vitrectomy.** UCSD at Vacation Village, San Diego. Friday-Saturday.

September 28-October 2—**American Academy of Otolaryngology.** Convention Center, Anaheim. Sunday-Thursday. Contact: AAO, 15 Second St. SW, Rochester, MN 55901.

October 3-5—**State of the Art: Recent Advances in Head and Neck Surgery.** Institute for Medical Education and Research at Islandia Hyatt, San Diego. Friday-Sunday. 14 hrs. $200. Contact: Inst. for Med. Ed. and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126 or (714) 294-5910.

October 9-11—**New Techniques in Hip Resurfacing and Replacement—In-depth Course and Workshop.** UCLA. Thursday-Saturday.

October 25-November 1—**Operative Arthroscopy.** UCLA at Maui, Hawaii. One week.

November 14-15—**Vitrectomy/Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs. $450.

December 11-13—**Trauma.** No. Calif. Chap. of the Committee on Trauma of Am. College of Surgeons at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. Contact: Donald D. Trunkey, MD, Chief of Surgery, S.F. Gen. Hosp., 1001 Potrero Ave., San Francisco 94110.

December 12-13—**Ophthalmology Update.** UCD, UCSF, PMC, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

OF INTEREST TO ALL PHYSICIANS

June 16-21—**Family Practice Refresher Course.** UCI at Marriott Inn, Newport Beach. Monday-Saturday. 50 hrs. $375. Contact: UCI (714) 833-5526.

June 21-22—**Risk—And the Health of the Public.** UCSF. Saturday-Sunday. $100. Contact: UCSF, Cont. Ed. in Health Sciences, 24 Kirkham, San Francisco 94143. (415) 666-3904.

June 22—**Physician/Pharmacist Dialogue Conference on Geriatric Drug Therapy.** Mount Zion Hosp., S.F. Dept. of Public Health, S.F. Pharmacists' Soc., S.F. Commission on the Aging at Mount Zion Hosp., San Francisco. Sunday. 6 hrs. $10. Contact: Kathryn Eng, S.F. Dept. of Public Health, 101 Grove St., San Francisco 94102. (415) 558-4343.

July 9-13—**Human Sexuality.** Associated Alumni, UCI, at Del Monte Hyatt, Monterey. Wednesday-Sunday. 15 hrs. Contact: June Harris, Associated Alumni, UCI-CCM, 101 City Dr. S., Bldg. 53, Orange 92668. (714) 634-0152.

July 25-26—**Symposium on Fundamentals of Occupational Medicine for Physicians.** UCI at Marriott, Newport Beach. Friday-Saturday. 13 hrs. Contact: Joan Brown, Calif. So. Ctr. for Occupational Health and Safety, UCI, College of Medicine, Community and Environmental Med., Irvine 92717. (714) 833-7241.

August 4-9—**Third Annual Gerontology Institute—Session II.** San Jose State Univ., San Jose. Monday-Saturday. Contact: Office of Cont. Ed., San Jose State Univ., San Jose 95192. (408) 277-2182.

August 10-14—**Western Hemisphere Nutrition Congress VI.** American Medical Association, American Institute of Nutrition, Nutrition Society of Canada, at Biltmore Hotel, Los Angeles. Sunday-Thursday. Contact: AMA, Dept. of Foods and Nutrition, 535 N. Dearborn St., Chicago 60610.

August 14-17—**Sexuality.** Orange County and American Urological Associations at Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

August 16-27—**23rd Annual Hawaii Refresher Course.** USC at Sheraton-Waikiki Hotel, Maui. 12 days. 39 hrs. $350.

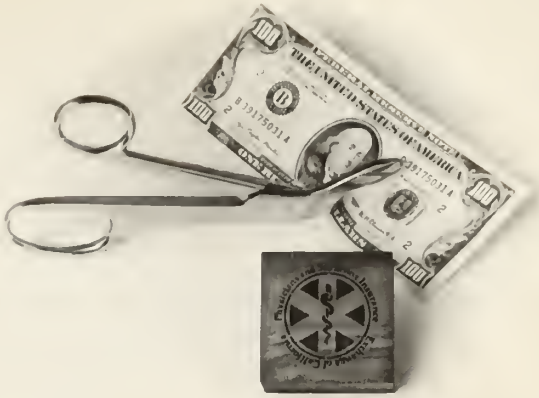
August 17-18—**Computers in Medicine—Applications of Artificial Intelligence Techniques.** STAN. Sunday-Monday. 11½ hrs. $40. Contact: William J. Clancey, AIM Tutorial Coordinator, Rm. TC 117, Div. of Gen. Int. Med., Stanford Univ. Sch. of Med., Stanford 94305.

August 23-28—**Practical Management of the Infertile Couple—4th Annual Edward Tyler Symposium.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. Saturday-Thursday. 16 hrs. $225. Contact: Jetset Tours, 2029 Century Park East, Suite 2130, Los Angeles 90067.

August 24-29—**Family Practice Refresher Course—8th Annual.** UCD at Del Monte Hyatt, Monterey. Sunday-Friday.

September 6—**Drug Abuse.** UCLA. Saturday.

September 24-27—**Society for Computer Medicine.** Hilton, San Diego. Wednesday-Saturday. Contact: SCM, 1901 N. Ft. Myer Dr., Ste. 602, Arlington, VA 22209.



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September 24-28—**Human Dimensions in Medicine.** UCSD at Vacation Village, San Diego. Wednesday-Sunday.

September 25—**Venereal Disease.** Calif. Venereal Disease Controllers' Assn. and CMA at Tiburon Lodge, Tiburon. Thursday. Contact: Manuel De Pinna, CMA.

September 26-27—**Dermatology for Physicians in Family Practice.** UCD at Holiday Inn, Napa Valley. Friday-Saturday.

September 29-October 1—**Alcoholism and Chemical Dependency Treatment—Where Do We Go From Here?** Scripps Memorial Hosp. at Vacation Village, San Diego. Monday-Wednesday. 15 hrs. $175. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110.

October 11—**Ophthalmology for the Family Physician.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

October 13-16—**Fifth Annual Family Practice Update.** LLU. Monday-Thursday. 31 hrs. $200.

October 13-17—**Hawaii Medical Association—124th Annual Meeting.** Pacific Beach Hotel, Waikiki. Monday-Friday. Contact: HMA, 320 Ward Ave., Ste. 200, Honolulu 96814. (808) 536-7702.

October 15-18—**24th Annual Western Occupational Health Conference.** Western Occupational Med. Assn. at Hotel del Coronado, Coronado. Wednesday-Saturday. Contact: Joe Donovan, WOHC, 433 Palmer Ave., Aptos 95003. (408) 688-9667.

October 16-18—**West Coast Counties Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 24-25—**Geriatric Medicine Today.** Western Div., Am. Geriatrics Soc., at Hyatt Regency, San Francisco. Friday-Saturday. Contact: AGS, Western Div., 13220 105th Ave., Bldg. B, Rm. 61, Sun City, AZ 85351.

October 25-26—**Eight Common Problems.** UCLA. Saturday-Sunday.

October 28-31—**American Academy of Occupational Medicine.** Hyatt Regency, San Francisco. Tuesday-Friday. Contact: AAOM, 150 N. Wacker Dr., Chicago 60606.

October 30-November 1—**Postgraduate Institute on Nutrition.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

November 3-7—**Postgraduate Institute for Primary Care Physicians.** UCSD at Hilton, San Diego. Monday-Friday. 27 hrs. $275.

November 3-7—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $290.

November 15—**Criteria for Evaluating Pseudoscience, Cults and Holistic Medicine.** San Jose State University. Saturday. 8 hrs. $40. Contact: Susan M. Grube, MPH, Cont. Ed., San Jose State Univ., Washington Sq., San Jose 95192. (408) 277-3778.

November 21-23—**Sports Medicine: The Physician and the Injured Athlete.** UCD at Marriott Inn, Berkeley. Friday-Sunday. 12 hrs.

November 21-25—**Gerontological Society—Annual Scientific Meeting.** Town and Country Hotel, San Diego. Friday-Tuesday. Contact: Dr. Eugene J. Towbin, VA Hospital, Little Rock, AR 72206.

December 5-7—**Human Sexuality.** Cypress Foundation and UCSF at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Robert S. Meyer, Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

June 19—**Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99504. (907) 274-7579.

August 13—**OB-GYN Sessions—Univ. of Washington** (Anchorage). Wednesday. Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 277-6891.

MONTANA

June 18-21—**Montana Academy of Family Physicians 30th Scientific Assembly.** Wednesday-Saturday. Fairmont Hot Springs. Contact: Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

IDAHO

August 22—**Intermountain Infectious Disease Symposium.** Idaho Falls. Friday. Intermountain Experience Center. Contact: DeVon Hale, MD, P.O. Box 1602, Idaho Falls, ID 83401. (208) 529-0072.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

MEDICINE

September 5-6—**Current Perspectives on Rheumatology.** Ashland, Friday-Saturday. Ashland Hills Inn. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

November 14-15—**Symposium on Critical Care Medicine.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

October 23-25—**Northwest Review of Obstetrics & Gynecology.** Portland, Thursday-Saturday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

PSYCHIATRY

September 13—**Movement Disorders.** Portland, Saturday. OMA Headquarters, 5210 SW Corbett Ave., Portland, OR 97201. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

June 17-20—**American College of Physicians Review Course.** Portland, Tuesday-Friday. Jantzen Beach Thunderbird. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

June 26-28—**Symposium on Sports Medicine.** Eugene, Thursday-Saturday. Thunderbird Motor Inn. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

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September 18-19—**Dermatology for the Non-Dermatologist.** Portland, Thursday-Friday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

June 19-20—**Perspectives in Clinical Chemistry.** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 23—**Basic Concepts of Immunology and Their Application—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

June 26-27—**American College of Physicians Medical Knowledge Self-Assessment Program V (MKSAP V).** Seattle. Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 28-July 5—**Alaska Cruise—Emergency Medical Care: Trauma, Orthopedics and Surgery; Biomedical History.** 8 days. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

July 25-26—**Seafair II Anesthesia Meeting**—Washington State Society of Anesthesiologists. Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Sandra McDonald, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

September 21-23—**Emergency Medicine in Office Practice.** Walla Walla. Sunday-Tuesday. Walla Walla General Hospital. Contact: Max W. Hammonds, MD, Director, Continuing Medical Education, Walla Walla General Hospital, 1025 South Second Avenue, P.O. Box 1398, Walla Walla, WA 99362. (509) 525-0480.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

June 16-19

SPONSOR: University of Utah
TITLE: **Physicians' Workshop on Alcoholism**
LOCATION: UU
FEE: $200.00
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

June 16-20

SPONSOR: VA Regional Medical Education Center
TITLE: **Legal Medicine**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Lew Erschler (801) 582-1565, Ext. 1100

July 10-11

SPONSOR: University of Utah
TITLE: **3rd Annual Birth Defects, Mental Retardation and Medical Genetics Symposium**
LOCATION: A. Ray Olpin Hall, University of Utah
FEE: $40.00
CREDIT: 13 hours
CONTACT: John Carey, MD (801) 581-8943

July 25-26

SPONSOR: Iron County Medical Society
TITLE: **11th Annual Iron County Medical Society Meeting**
LOCATION: Cedar City, Utah
FEE: To be announced
CREDIT: To be announced
CONTACT: J. Garth Chatterley, MD (801) 586-9447

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Carbon Hospital, Washington Park, Price 84501. (801) 637-1123
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84107 (801) 262-3461
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UU: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

August 1-9

SPONSOR: University of Utah
TITLE: **2nd Annual Postgraduate Radiology Conference**
LOCATION: Veendam Cruise—Vancouver to Alaska
FEE: $300.00
CREDIT: 33 hours
CONTACT: David G. Bragg, MD (801) 581-8188

August 7-8

SPONSOR: VA Regional Medical Education Center
TITLE: **Geriatric Assessment**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Barbara Cordell, RN (801) 582-1565, Ext. 1100

August 8-9

SPONSOR: Utah Ophthalmological Society
TITLE: **Annual Shakespeare Festival Meeting**
Speaker: Frederick H. Reeser, MD, Medical College of Wisconsin, Milwaukee
LOCATION: Town & Country Inn, Cedar City, Utah
FEE: Members $40.00
Non-members $75.00
CREDIT: 6 hours
CONTACT: A. Thomas Williams, MD (801) 268-6111

August 15

SPONSOR: University of Utah
TITLE: **Antimicrobial Agents in Serious Infections in the Immunocompromised Host**
LOCATION: Classroom A, University Medical Center
FEE: None
CREDIT: 7 hours
CONTACT: Charles Smith, MD (801) 581-8811

August 26-28

SPONSOR: VA Regional Medical Education Center
TITLE: **Conflict, Confrontation, and Stress**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Alan Lundgren (801) 582-1565, Ext. 1100

September 11

SPONSOR: Rocky Mountain Center for Occupational and Environmental Health
TITLE: **Occupational Health for the 1980's**
LOCATION: Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

September 12

SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Medical Management of Ischemic Heart Disease**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: 3 hours
CONTACT: Stan Everett (801) 350-1004

September 18-20

SPONSOR: University of Utah
TITLE: **Preceptor Teaching Skills**
LOCATION: Snowbird, Utah
FEE: $15.00
CREDIT: 10.5 hours
CONTACT: Donna Harris (801) 581-8250

September 22-25

SPONSOR: VA Regional Medical Education Center
TITLE: **Sexual Health**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: George Keiser, PhD (801) 582-1565, Ext. 1100

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WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1981—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: 1981—date and place to be announced.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 24-27, 1980, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 13-17, 1980, Pacific Beach Hotel, Waikiki.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1980, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 2-4, 1980, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: 1981—date and place to be announced.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: 1981—date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-31, 1980, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 30-October 3, 1980, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 2-5, 1980, Thunderbird at Jantzen Beach, Vancouver, WA.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 23-27, 1980, Snow King Inn, Jackson.

September 30-October 3

SPONSOR: University of Utah
TITLE: **Utah State Medical Association Scientific Meeting**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: Up to 12 hours
CONTACT: Maxcine Fry (801) 355-7477

October 1-2

SPONSOR: VA Regional Medical Education Center
TITLE: **Geriatric Assessment**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Barbara Cordell, RN (801) 582-1565, Ext. 1100

October 10-11

SPONSOR: University of Utah/The Upjohn Company
TITLE: **2nd Fall Arthritis Conference—Clinical Assessment and Management of Back Pain**
LOCATION: Park City, Utah
FEE: $70.00
CREDIT: 11 hours
CONTACT: Mark Mueller, MD (801) 581-7724

October 16

SPONSOR: LDS Hospital (with Intermountain Thoracic Society, Utah Heart Association and University of Utah)
TITLE: **Postgraduate Course—Pulmonary Heart Disease**
LOCATION: LDSH
FEE: To be announced
CREDIT: 6 hours
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

December 12

SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Hypertension**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: To be announced
CONTACT: Stan Everett (801) 350-1004

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

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